FORM PTO-1390 (Modified) (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 049441-0127

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/889858 Unassigned

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/00255	January 20, 2000	January 22, 1999

TITLE OF INVENTION
QUINOLINE DERIVATIES AND QUINAZOLINE DERIVATIVES

APPLICANT(S) FOR DO/EO/US
Kazuo KUBO, Yasunari FUJIWARA and Toshiyuki ISOE

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ has been transmitted by the International Bureau.
   - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
11. ☐ Applicant claims small entity status under 37 CFR 1.27 .

Items 12. to 17. below concern other document(s) or information included:

12. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
14. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Unassigned 09/889858	PCT/JP00/00255	049441-0127

18. ☒ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO $860.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1,000.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))		

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate	
Total Claims	52	-	20	=	32	×	$18.00	$576.00
Independent Claims	2	-	3	=	0	×	$80.00	$0.00
Multiple dependent claim(s) (if applicable)							$270.00	
TOTAL OF ABOVE CALCULATIONS =								$1,576.00
Reduction by ½ for filing by small entity, if applicable.								$0.00
SUBTOTAL =								$1,576.00
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +								
TOTAL NATIONAL FEE =								$1,576.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +								$40.00
TOTAL FEES ENCLOSED =								$1,616.00
							Amount to be: refunded	$
							charged	$

a. ☒ A check in the amount of $1,616.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $0.00 to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Foley & Lardner
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109

SIGNATURE

NAME STEPHEN A. BENT

REGISTRATION NUMBER 29,768

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kazuo KUBO et al.

Title: QUINOLINE DERIVATIES AND QUINAZOLINE DERIVATIVES

Prior Appl. No.: PCT/JP00/00255

Prior Appl. Filing Date: January 20, 2000

Examiner: Unassigned

Art Unit: Unassigned

PRELIMINARY AMENDMENT

Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Sir:

Prior to examination of the present Application, Applicant respectfully requests that the application be amended as follows:

IN THE SPECIFICATION:

Please amend the specification as follows:

After the Application Title, please insert: --This is a U.S. National Phase application of PCT/JP00/002555 filed January 20, 2000--.

Please replace the following paragraphs with the following rewritten paragraphs. The changes are shown explicitly in the attached "Version with Markings to Show Changes Made."

Please replace the paragraph beginning on page 15 at lines 18, 21 and 23 with the following rewritten paragraphs respectively:

(145) N-[2-chloro-4-({6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N′-propylurea

(146) N-[2-chloro-4-({7-[2-(1H-1-imidazolyl)-ethoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N′-propylurea

(148) N-[2-chloro-4-({6-methoxy-7-[2-(4-methyl-piperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N′-propylurea.

Please replace the paragraph beginning on page 16 at lines 4, 12 and 24 with the following rewritten paragraphs respectively:

(160) N-[2-Chloro-4-({7-[4-(1H-1-imidazolyl)-butoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N′-propylurea

(164) N-[2-chloro-4-({6-methoxy-7-[3-(4-methyl-piperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N′-(2,4-difluorophenyl)urea

(170) N-[2-chloro-4-({6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N′-(2,4-difluorophenyl)urea.

IN THE CLAIMS:

In accordance with 37 CFR §1.121, please substitute for original claims 21-25, 28-32, 35-39, 42-46, 47-48, and 50-52 the following rewritten versions of the same claims, as amended. The changes are shown explicitly in the attached "Versions With Markings to Show Changes Made."

21. (Amended) The compound according to claim 19, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

22. (Amended) The compound according to claim 19, wherein p is 1.

23. (Amended) The compound according to claim 19, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

24. (Amended) The compound according to claim 19, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

25. (Amended) The compound according to claim 23, wherein R^{14} represents optionally substituted pyridyl.

28. (Amended) The compound according to claim 26, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

29. (Amended) The compound according to claim 26, wherein p is 1.

30. (Amended) The compound according to claim 26, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

31. (Amended) The compound according to claim 26, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered

heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

32. (Amended) The compound according to claim 30, wherein R^{14} represents optionally substituted pyridyl.

35. (Amended) The compound according to claim 33, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

36. (Amended) The compound according to claim 33, wherein p is 1.

37. (Amended) The compound according to claim 33, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

38. (Amended) The compound according to claim 33, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

39. (Amended) The compound according to claim 37, wherein R^{14} represents optionally substituted pyridyl.

42. (Amended) The compound according to claim 40, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic

group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

43. (Amended) The compound according to claim 40, wherein p is 1.

44. (Amended) The compound according to claim 40, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

45. (Amended) The compound according to claim 40, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

46. Amended) The compound according to claim 44, wherein R^{14} represents optionally substituted pyridyl.

47. (Amended) The compound according to claim 1, which is a compound selected from the group consisting of the following compounds, or a pharmaceutically acceptable salt or solvate thereof:

(13) N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(51) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl) urea;

(62) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-propylurea;

(76) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-ethylurea;

(117) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazo-linyl)oxy]phenyl}-N'-methylurea;

(119) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

(135) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea; (142) N-(2-chloro-4-{[6-methoxy-7-(3-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(143) N-(2-chloro-4-{[6-methoxy-7-(4-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(144) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(145) N-[2-chloro-4-({6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(146) N-[2-chloro-4-(7-{[2-(1H-1-imidazolyl)-ethoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(148) N-[2-chloro-4-({6-methoxy-7-{[2-(4-methyl-piperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(149) N-(2-chloro-4-{[7-(2-hydroxyethoxy)-6-methoxy-4-quinolyl]oxy}phenyl)-N'-propylurea;

(151) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(152) N-[2-chloro-4-(6-methoxy-7-{[3-(4-methyl-piperazino)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(153) N-[2-chloro-4-(6-methoxy-7-{[3-(1*H*-1,2,3-triazol-1-yl)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(157) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(159) N-{2-chloro-4-[(6-methoxy-7-{[5-(1*H*-1,2,3-triazol-1-yl)pentyl]oxy}-4-quinolyl)oxy]phenyl}-N'-propylurea;

(160) N-[2-chloro-4-({7-[4-(1*H*-1-imidazolyl)-butoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(162) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(163) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(164) N-[2-chloro-4-({6-methoxy-7-[3-(4-methyl-piperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(165) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinazolinyl)oxy]-phenyl}-N'-(2,4-difluorophenyl)urea;

(168) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(169) N-(2-chloro-4-{[6-methoxy-7-(3-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(170) N-[2-chloro-4-({6-methoxy-7-[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(184) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-methylurea;

(185) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-ethylurea; and

(186) N-(2-chloro-4-{[6-methoxy-7-(4-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea.

48. (Amended) A pharmaceutical composition comprising as active ingredient the compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof.

50. (Amended) Use of the compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a therapeutic agent for use in the treatment of a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma.

51. (Amended) A method for treating a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, comprising the step of administering an effective amount of the compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier, to mammals.

52. (Amended) A method for inhibiting the angiogenesis of target blood vessels, comprising the step of making the compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof in contact with vascular endothelial cells of the target blood vessels.

REMARKS

Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application.

After amending the claims as set forth above, claims 1-52 are now pending in this application.

Applicant believes that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date July 23, 2001

By _____

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768

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Versions with Markings to Show Changes Made

Page 15 at lines 18, 21 and 23 with the following rewritten paragraphs respectively:

(145) N-[2-chloro-4-({6-methoxy-7-[{][2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N´-propylurea

(146) N-[2-chloro-4-({7-[{][2-(1H-1-imidazolyl)-ethoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N´-propylurea

(148) N-[2-chloro-4-({6-methoxy-7-[{][2-(4-methyl-piperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N´-propylurea.

Page 16 at lines 4, 12 and 24 with the following rewritten paragraphs respectively:

(160) N-[2-Chloro-4-({7-[{][4-(1H-1-imidazolyl)-butoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N´-propylurea

(164) N-[2-chloro-4-({6-methoxy-7-[{][3-(4-methyl-piperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N´-(2,4-difluorophenyl)urea

(170) N-[2-chloro-4-({6-methoxy-7-[{][2-(1H-1,2,3-triazol-l-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N´-(2,4-difluorophenyl)urea.

IN THE CLAIMS:

21. (Amended) The compound according to claim 19 [or 20], wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

22. (Amended) The compound according to [any one of claims 19 to 21] claim 19, wherein p is 1.

23. (Amended) The compound according to [any one of claims 19 to 21] claim 19, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

24. (Amended) The compound according to [any one of claims 19 to 21] claim 19, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

25. (Amended) The compound according to claim 23 [or 24], wherein R^{14} represents optionally substituted pyridyl.

28. (Amended) The compound according to claim 26 [or 27], wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

29. (Amended) The compound according to [any one of claims 26 to 28] claim 26, wherein p is 1.

30. (Amended) The compound according to [any one of claims 26 to 28] claim 26, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

31. (Amended) The compound according to [any one of claims 26 to 28] claim 26, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

32. (Amended) The compound according to claim 30 [or 31], wherein R^{14} represents optionally substituted pyridyl.

35. (Amended) The compound according to claim 33 [or 34], wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

36. (Amended) The compound according to [any one of claims 33 to 35] claim 33, wherein p is 1.

37. (Amended) The compound according to [any one of claims 33 to 35] claim 33, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

38. (Amended) The compound according to [any one of claims 33 to 35] claim 33, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

39. (Amended) The compound according to claim 37 [or 38], wherein R^{14} represents optionally substituted pyridyl.

42. (Amended) The compound according to claim 40 [or 41], wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

43. (Amended) The compound according to [any one of claims 40 to 42] claim 40, wherein p is 1.

44. (Amended) The compound according to [any one of claims 40 to 42] claim 40, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

45. (Amended) The compound according to [any one of claims 40 to 42] claim 40, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

46. (Amended) The compound according to claim 44 [or 45], wherein R^{14} represents optionally substituted pyridyl.

47. (Amended) The compound according to claim 1, which is a compound selected from the group consisting of the following compounds, or a pharmaceutically acceptable salt or solvate thereof:

(13) N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(51) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl) urea;

(62) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-propylurea;

(76) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-ethylurea;

(117) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazo-linyl)oxy]phenyl}-N'-methylurea;

(119) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

(135) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea; (142) N-(2-chloro-4-{[6-methoxy-7-(3-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(143) N-(2-chloro-4-{[6-methoxy-7-(4-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(144) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(145) N-[2-chloro-4-({6-methoxy-7-[{][2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(146) N-[2-chloro-4-({7-[{] [2-(1H-1-imidazolyl)-ethoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(148) N-[2-chloro-4-({6-methoxy-7-[{][2-(4-methyl-piperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(149) N-(2-chloro-4-{[7-(2-hydroxyethoxy)-6-methoxy-4-quinolyl]oxy}phenyl)-N'-propylurea;

(151) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(152) N-[2-chloro-4-(6-methoxy-7-{[3-(4-methyl-piperazino)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(153) N-[2-chloro-4-(6-methoxy-7-{[3-(1*H*-1,2,3-triazol-1-yl)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(157) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(159) N-{2-chloro-4-[(6-methoxy-7-{[5-(1*H*-1,2,3-triazol-1-yl)pentyl]oxy}-4-quinolyl)oxy]phenyl}-N'-propylurea;

(160) N-[2-chloro-4-({7-[{][4-(1*H*-1-imidazolyl)-butoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(162) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(163) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(164) N-[2-chloro-4-({6-methoxy-7-[{][3-(4-methyl-piperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(165) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinazolinyl)oxy]-phenyl}-N'-(2,4-difluorophenyl)urea;

(168) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(169) N-(2-chloro-4-{[6-methoxy-7-(3-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(170) N-[2-chloro-4-({6-methoxy-7-[{][2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(184) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-methylurea;

(185) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-ethylurea; and

(186) N-(2-chloro-4-{[6-methoxy-7-(4-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea.

48. (Amended) A pharmaceutical composition comprising as active ingredient the compound according to [any one of claims 1 to 47] claim 1 or a pharmaceutically acceptable salt or solvate thereof.

50. (Amended) Use of the compound according to [any one of claims 1 to 47] claim 1 or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a therapeutic agent for use in the treatment of a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma.

51. (Amended) A method for treating a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, comprising the step of administering an effective amount of the compound according to [any one of claims 1 to 47] claim 1 or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier, to mammals.

52. (Amended) A method for inhibiting the angiogenesis of target blood vessels, comprising the step of making the compound according to [any one of claims 1 to 47] claim 1 or a pharmaceutically acceptable salt or solvate thereof in contact with vascular endothelial cells of the target blood vessels.

QUINOLINE DERIVATIVES AND QUINAZOLINE DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to quinoline derivatives and quinazoline derivatives having antitumor activity. More particularly, the present invention relates to quinoline derivatives and quinazoline derivatives that are useful for the treatment of diseases such as tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma.

Background Art

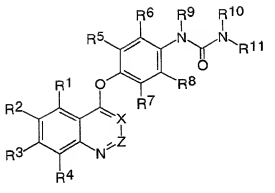
WO 97/17329 describes quinoline derivatives and quinazoline derivatives having antitumor activity. WO 97/17329, however, discloses neither the effects of these quinoline derivatives and quinazoline derivatives on cytomorphosis nor the compounds according to the present invention.

SUMMARY OF THE INVENTION

The present inventors have found that a group of quinoline derivatives and quinazoline derivatives has antitumor activity and, at the same time, has no significant effect on cytomorphosis. The activity of increasing the cell size may be regarded as activity of inducing tissue disorders.

An object of the present invention is to provide compounds which have antitumor activity and, at the same time, have no significant effect on cytomorphosis.

According to the present invention, there is provided a compound represented by formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

X and Z each represent CH or N;

R^1, R^2, and R^3, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, nitro, or amino, which C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted by a halogen atom; hydroxyl; C_{1-4} alkoxy; C_{1-4} alkoxycarbonyl; amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl or C_{1-4} alkoxy; group $R^{12}R^{13}N$-C(=O)-O- wherein R^{12} and R^{13}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkyl which alkyl is optionally substituted by hydroxyl or C_{1-4} alkoxy; or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group optionally substituted by C_{1-4} alkyl and m is 0 or 1;

R^4 represents a hydrogen atom;

R^5, R^6, R^7, and R^8, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino, provided that R^5, R^6, R^7, and R^8 do not simultaneously represent a hydrogen atom;

R^9 and R^{10}, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, or C_{1-4} alkylcarbonyl, the alkyl portion of which C_{1-6} alkyl or C_{1-4} alkylcarbonyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted

by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group; and

R^{11} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-6} alkoxy), or R^{15}-(CH_2)n- wherein n is an integer of 0 to 4 and R^{15} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-6} alkyl, or C_{1-6} alkoxy and is optionally condensed with other saturated or unsaturated three- to seven-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

The compound according to the present invention is useful, for example, for the treatment of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, Kaposi's sarcoma, and solid tumor.

DETAILED DESCRIPTION OF THE INVENTION

Compound

As used herein, the term "C_{1-6} alkyl" and "C_{1-6} alkoxy" as a group or a part of a group respectively mean straight chain or branched chain alkyl and alkoxy having 1 to 6, preferably 1 to 4 carbon atoms.

As used herein, the term "C_{2-6} alkenyl" and "C_{2-6} alkynyl" as a group or a part of a group respectively mean straight chain or branched chain alkenyl and alkynyl having 2 to 6, preferably 2 to 4 carbon atoms.

Examples of C_{1-6} alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, and n-hexyl.

Examples of C_{1-6} alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, and t-butoxy.

Examples of C_{2-6} alkenyl include allyl, butenyl, pentenyl, and hexenyl.

Examples of C_{2-6} alkynyl include 2-propynyl, butynyl, pentynyl, and hexynyl.

The term "halogen atom" means a fluorine, chlorine, bromine, or iodine atom.

The saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic ring is preferably five- to seven-membered, more preferably five- or six-membered, saturated or unsaturated carbocyclic or heterocyclic ring.

Examples of saturated or unsaturated three- to seven-membered carbocyclic groups include phenyl, cycloheptyl, cyclohexyl, and cyclopentyl.

The saturated or unsaturated three- to seven-membered heterocyclic ring contains at least one hetero-atom selected from oxygen, nitrogen, and sulfur atoms. The term "hetero-atom" used herein means an oxygen, nitrogen, or sulfur atom. Examples of saturated or unsaturated three- to seven-membered heterocyclic groups include pyridyl, piperidino, piperazino, morpholino, imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, pyrrolidinyl, and pyrazolyl.

The saturated or unsaturated heterocyclic group, which may be represented by R^{15} and R^{32}, may be condensed with other saturated or unsaturated heterocyclic ring to form a bicyclic ring. Such condensed cyclic groups include naphthyl, indanyl, quinolyl, and quinazolinyl.

R^1 preferably represents a hydrogen atom.

R^2 and R^3 preferably represents optionally substituted C_{1-6} alkoxy.

C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, and C_{2-6} alkynyl, which may be represented by R^1, R^2, and R^3, may be substituted by group R^{14}-(S)m-.

The carbocyclic or heterocyclic group, which may be represented by R^{14}, preferably represents a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group. The carbocyclic group more preferably represents phenyl. The heterocyclic group

more preferably represents a saturated or unsaturated five-membered heterocyclic group containing one to four nitrogen atoms or a saturated or unsaturated six-membered heterocyclic group (preferably pyridyl) containing one or two hetero-atoms selected from nitrogen and oxygen atoms. More specifically, the hetero-atom constituting the six-membered heterocyclic group may be one nitrogen atom and one oxygen atom, or one or two nitrogen atoms.

When m is 0 (zero), -(S)m- represents a bond.

The substituted C_{1-6} alkoxy group, which may be represented by R^1, R^2, and R^3, preferably represents group R^{31}-(CH_2)p-O- wherein R^{31} represents a halogen atom, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, amino on which one or two hydrogen atoms each are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl or C_{1-4} alkoxy, group $R^{12}R^{13}N$-C(=O)-O- wherein R^{12} and R^{13} are as defined in formula (I), or group R^{14}-(S)m- wherein R^{14} may be as defined in formula (I); p is an integer of 1 to 6, preferably 1 to 4, more preferably 1 or 2, particularly preferably 1.

A group of preferred compounds represented by formula (I) include:

compounds wherein R^1 represents a hydrogen atom and R^2 and R^3 represent unsubstituted C_{1-4} alkoxy, preferably methoxy;

compounds wherein R^1 represents a hydrogen atom, R^2 represents substituted C_{1-4} alkoxy, preferably group R^{31}-(CH_2)p-O-, and R^3 represents unsubstituted C_{1-4} alkoxy, preferably methoxy; and

compounds wherein R^1 represents a hydrogen atom, R^2 represents unsubstituted C_{1-4} alkoxy, preferably methoxy, and R^3 represents substituted C_{1-4} alkoxy, preferably group R^{31}-(CH_2)p-O-.

Another group of preferred compounds represented by formula (I) include:

compounds wherein at least one of R^5, R^6, R^7, and R^8

represents a halogen atom, preferably a chlorine atom or a fluorine atom;

compounds wherein at least one of R^5, R^6, R^7, and R^8 represents C_{1-4} alkyl;

compounds wherein two of R^5, R^6, R^7, and R^8 represent methyl and the remaining two represent a hydrogen atom;

compounds wherein at least one of R^5, R^6, R^7, and R^8 repersents nitro, amino, C_{1-4} alkoxy, or C_{1-4} alkylthio;

compounds wherein R^5, R^7, and R^8 represent a hydrogen atom and R^6 represents a halogen atom, more preferably a chlorine atom or a fluorine atom;

compounds wherein R^5 and R^6 represent C_{1-4} alkyl, more preferably methyl, and R^7 and R^8 represent a hydrogen atom;

compounds wherein R^5 and R^8 represent a hydrogen atom and R^6 and R^7 represent C_{1-4} alkyl, more preferably methyl; and

compounds wherein R^5, R^7, and R^8 represent a hydrogen atom and R^6 represents C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino.

In R^9 and R^{10}, the saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group as the substituent preferably represents a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group.

R^9 and R^{10} preferably represent a hydrogen atom, methyl, ethyl, propyl, methoxymethyl, formyl, acetyl, benzyl, or phenetyl.

Still another group of preferred compounds represented by formula (I) include:

compounds wherein R^1, R^9, and R^{10} represent a hydrogen atom; and

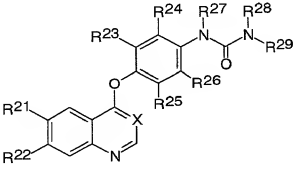
compounds wherein R^1 represents a hydrogen atom and any one of or both R^9 and R^{10} represent a group other than a hydrogen atom.

In group R^{15}-$(CH_2)n$- which may be represented by R^{11},

n is preferably an integer of 0 to 2, more preferably 0 or 1. Preferred examples of R^{15} include an optionally substituted saturated or unsaturated six-membered carbocyclic group, more preferably phenyl, and an optionally substituted saturated or unsaturated six-membered heterocyclic group, more preferably pyridyl. The hetero-atom(s) constituting the six-membered heterocyclic group may more specifically consist of one nitrogen atom or one nitrogen atom and one oxygen atom.

A further group of preferred compounds represented by formula (I) include compounds wherein X represents N or CH and Z represents CH.

A still further group of preferred compounds represented by formula (I) include compounds represented by formula (Ia):



(Ia)

wherein

X represents CH or N;

R^{21} and R^{22}, which may be the same or different, represent unsubstituted C_{1-6} alkoxy or group R^{31}-(CH_2)p-O- wherein R^{31} represents a halogen atom, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl or C_{1-4} alkoxy, group $R^{12}R^{13}N$-C(=O)-O- wherein R^{12} and R^{13}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkyl which alkyl is optionally substituted by hydroxyl or C_{1-4} alkoxy, or group R^{14}-(S)m- wherein R^{14} represents a

saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group optionally substituted by C_{1-4} alkyl and m is 0 or 1; and p is an integer of 1 to 6;

R^{23}, R^{24}, R^{25}, and R^{26}, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino, provided that R^{23}, R^{24}, R^{25}, and R^{26} do not simultaneously represent a hydrogen atom;

R^{27} and R^{28}, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, or C_{1-4} alkylcarbonyl, the alkyl portion of which C_{1-6} alkyl or C_{1-4} alkylcarbonyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or R^{32}-$(CH_2)q$- wherein q is an integer of 0 to 4 and R^{32} represents a saturated or unsaturated six-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy and is optionally condensed with other saturated or unsaturated five- or six-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

R^{21} and R^{22} may represent unsubstituted C_{1-6} alkoxy, preferably methoxy.

Any one of R^{21} and R^{22} may represent unsubstituted C_{1-6} alkoxy, preferably methoxy and the other represents group R^{31}-$(CH_2)p$-O-.

In group R^{31}-$(CH_2)p$-O-, p is preferably 1 to 4, more preferably 1 or 2, particularly preferably 1.

A group of preferred compounds represented by formula (Ia) include:

compounds wherein at least one of R^{23}, R^{24}, R^{25}, and R^{26} represents a halogen atom, preferably a chlorine atom or a fluorine atom;

compounds wherein at least one of R^{23}, R^{24}, R^{25}, and R^{26} represents C_{1-4} alkyl;

compounds wherein two of R^{23}, R^{24}, R^{25}, and R^{26} represent methyl and the remaining two represent a hydrogen atom;

compounds wherein at least one of R^{23}, R^{24}, R^{25}, and R^{26} represents nitro, amino, C_{1-4} alkoxy, or C_{1-4} alkylthio;

compounds wherein R^{23}, R^{25}, and R^{26} represent a hydrogen atom and R^{24} represents a halogen atom, more preferably a chlorine atom or a fluorine atom;

compounds wherein R^{23} and R^{24} represent C_{1-4} alkyl, more preferably methyl and R^{25} and R^{26} represent a hydrogen atom;

compounds wherein R^{23} and R^{26} represent a hydrogen atom and R^{24} and R^{25} represent C_{1-4} alkyl, more preferably methyl; and

compounds wherein R^{23}, R^{25}, and R^{26} represent a hydrogen atom and R^{24} represents C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino.

Another group of preferred compounds represented by formula (Ia) include compounds wherein R^{27} and R^{28} represent a hydrogen atom.

Still another group of preferred compounds represented by formula (Ia) include compounds wherein any one of or both R^{27} and R^{28} represent a group other than a hydrogen atom.

In R^{32}-$(CH_2)q$- which may be represented by R^{29}, q is preferably an integer of 0 to 2, more preferably 0 or 1. Examples of preferred R^{32} include optionally substituted phenyl and an optionally substituted saturated or unsaturated six-membered heterocyclic group, more preferably pyridyl. The hetero-atom(s) constituting the six-membered heterocyclic group may more specifically consist of one nitrogen atom or one nitrogen atom and

one oxygen atom. The saturated or unsaturated six-membered carbocyclic group or heterocyclic group, which may be represented by R^{32}, is preferably condensed with other saturated or unsaturated six-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

A still further group of preferred compounds represented by formula (Ia) include:

compounds wherein

X represents CH or N,

R^{21} and R^{22} represent unsubstituted C_{1-4} alkoxy,

R^{23}, R^{25}, and R^{26} represent a hydrogen atom,

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro,

R^{27} and R^{28} represent a hydrogen atom, and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy;

compounds wherein

X represents CH or N,

R^{21} and R^{22} represent unsubstituted C_{1-4} alkoxy,

R^{23}, R^{25}, and R^{26} represent a hydrogen atom,

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro,

any one of or both R^{27} and R^{28} represent a group other than a hydrogen atom, and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy;

compounds wherein

X represents CH or N,

R^{21} and R^{22} represent unsubstituted C_{1-4} alkoxy,

R^{23}, R^{25}, and R^{26} represent a hydrogen atom,

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro,

R^{27} represents a hydrogen atom,

R^{28} represents a group other than a hydrogen atom, and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy;

compounds wherein

X represents CH or N,

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group $R^{31}-(CH_2)p-O-$, preferably R^{21} represents unsubstituted C_{1-4} alkoxy and R^{22} represents group $R^{31}-(CH_2)p-O-$,

R^{23}, R^{25}, and R^{26} represent a hydrogen atom,

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro,

R^{27} and R^{28} represent a hydrogen atom, and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy;

compounds wherein

X represents CH or N,

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group $R^{31}-(CH_2)p-O-$, preferably R^{21} represents unsubstituted C_{1-4} alkoxy and R^{22}

represents group R^{31}-$(CH_2)p$-O-,

R^{23}, R^{25}, and R^{26} represent a hydrogen atom,

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro,

any one of or both R^{27} and R^{28} represent a group other than a hydrogen atom, and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy;

compounds wherein

X represents CH or N,

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group R^{31}-$(CH_2)p$-O-, preferably R^{21} represents unsubstituted C_{1-4} alkoxy and R^{22} represents group R^{31}-$(CH_2)p$-O-,

R^{23}, R^{25}, and R^{26} represent a hydrogen atom,

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro,

R^{27} represents a hydrogen atom,

R^{28} represents a group other than a hydrogen atom, and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy; and

compounds wherein

X represents CH or N,

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group R^{31}-$(CH_2)p$-O-, preferably R^{21} represents unsubstituted C_{1-4} alkoxy and R^{22}

represents group R^{31}-$(CH_2)p$-O-,

R^{23} and R^{26} represent a hydrogen atom,

R^{24} and R^{25} represent a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro,

R^{27} and R^{28} represent a hydrogen atom, and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

Examples of preferred compounds according to the present invention include compounds described in Examples 1 to 186.

Another examples of preferred compounds according to the present invention include the following compounds:

N-{2-chloro-4-[(6,7-dimethyl-4-quinazolinyl)oxy]-phenyl}-N'-isobutylurea;

N-(4-{[7-(benzyloxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propylurea;

N-(4-{[6-(benzyloxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propylurea;

N-(2-chloro-4-{[7-methoxy-6-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(1H-1-imidazolyl)-ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-ethylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-ethylurea;

N-[2-chloro-4-({6-methoxy-7-[3-(1H-1,2,3-triazol-1-yl)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-ethylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(4-methyl-piperazino)ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-ethylurea;

N-(2-chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinazolinyl]oxy}phenyl)-N'-ethylurea;

N-(2-chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-ethylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(dimethylamino)-ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-ethylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(1H-1-imidazolyl)-ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea;

N-[2-chloro-4-({6-methoxy-7-[3-(1H-1,2,3-triazol-1-yl)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea;

N-(2-chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(dimethylamino)-ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(1H-1-imidazolyl)-ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-butylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-butylurea;

N-[2-chloro-4-({6-methoxy-7-[3-(1H-1,2,3-triazol-1-yl)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-butylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(4-methyl-piperazino)ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-butylurea;

N-(2-chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinazolinyl]oxy}phenyl)-N'-butylurea;

N-(2-chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-butylurea;

N-[2-chloro-4-({6-methoxy-7-[2-(dimethylamino)-ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-butylurea; and

N-[2-chloro-4-({6-methoxy-7-[2-(dimethylamino)-ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea.

Examples of particularly preferred compounds according to the present invention include:

(13) N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(51) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)

urea;

(62) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-propylurea;

(76) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-ethylurea;

(117) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-methylurea;

(119) N-(2-chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

(135) N-(2-chloro-4-{[6-methoxy-7-(3-piperidinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

(142) N-(2-chloro-4-{[6-methoxy-7-(3-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(143) N-(2-chloro-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(144) N-(2-chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(145) N-[2-chloro-4-(6-methoxy-7-{[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(146) N-[2-chloro-4-(7-{[2-(1H-1-imidazolyl)-ethoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(148) N-[2-chloro-4-(6-methoxy-7-{[2-(4-methylpiperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(149) N-(2-chloro-4-{[7-(2-hydroxyethoxy)-6-methoxy-4-quinolyl]oxy}phenyl)-N'-propylurea;

(151) N-(2-chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(152) N-[2-chloro-4-(6-methoxy-7-{[3-(4-methylpiperazino)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(153) N-[2-chloro-4-(6-methoxy-7-{[3-(1*H*-1,2,3-triazol-1-yl)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(157) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(159) N-{2-chloro-4-[(6-methoxy-7-{[5-(1*H*-1,2,3-triazol-1-yl)pentyl]oxy}-4-quinolyl)oxy]phenyl}-N'-propylurea;

(160) N-[2-chloro-4-(7-{[4-(1*H*-1-imidazolyl)-butoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(162) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(163) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(164) N-[2-chloro-4-(6-methoxy-7-{[3-(4-methyl-piperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(165) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinazolinyl)oxy]-phenyl}-N'-(2,4-difluorophenyl)urea;

(168) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(169) N-(2-chloro-4-{[6-methoxy-7-(3-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(170) N-[2-chloro-4-(6-methoxy-7-{[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(184) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-methylurea;

(185) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-ethylurea; and

(186) N-(2-chloro-4-{[6-methoxy-7-(4-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea.

Examples of more preferred compounds according to the present invention include the following compounds:

(62) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-propylurea;

(142) N-(2-chloro-4-{[6-methoxy-7-(3-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea; and

(169) N-(2-chloro-4-{[6-methoxy-7-(3-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea.

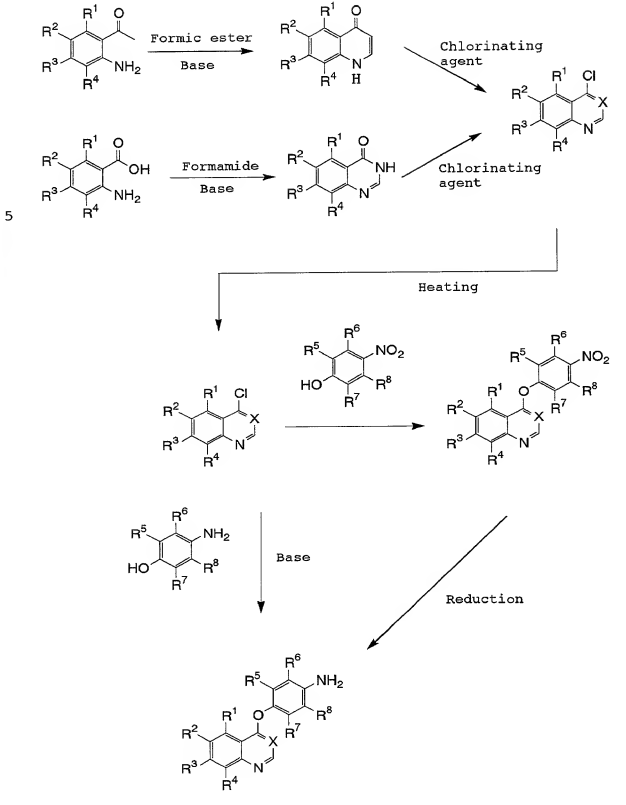
The compounds according to the present invention may form pharmaceutically acceptable salts thereof. Preferred examples of such salts include: alkali metal or alkaline earth metal salts such as sodium salts, potassium salts or calcium salts; hydrohalogenic acid salts such as hydrofluoride salts, hydrochloride salts, hydrobromide salts, or hydroiodide salts; inorganic acid salts such as nitric acid salts, perchloric acid salts, sulfuric acid salts, or phosphoric acid salts; lower alkylsulfonic acid salts such as methanesulfonic acid salts, trifluoromethanesulfonic acid salts, or ethanesulfonic acid salts; arylsulfonic acid salts such as benzenesulfonic acid salts or p-toluenesulfonic acid salts; organic acid salts such as fumaric acid salts, succinic acid salts, citric acid salts, tartaric acid salts, oxalic acid salts, maleic acid salts, acetic acid salts, malic acid salts, lactic acid salts, or ascorbic acid salts; and amino acid salts such as glycine salts, phenylalanine salts, glutamic acid salts, or aspartic acid salts.

Further, the compounds according to the present invention may form solvates (for example, hydrates).

Production of compounds

The compounds according to the present invention may be produced, for example, according to scheme 1 and scheme 2.

Scheme 1


Formic ester
Base
Chlorinating agent
Formamide
Base
Chlorinating agent
Heating
Base
Reduction

Starting compounds necessary for the synthesis of the compounds according to the present invention may be commercially available, or alternatively may be produced according to a conventional process. For example, a 4-chloroquinoline derivative may be synthesized by a conventional process as described in Org. Synth. Col. Vol. 3, 272 (1955), Acta Chim. Hung., 112, 241 (1983) or WO 98/47873. A 4-chloroquinazoline derivative may be synthesized by a conventional process as described in J. Am. Chem. Soc., 68, 1299 (1946) or J. Am. Chem. Soc., 68, 1305 (1946).

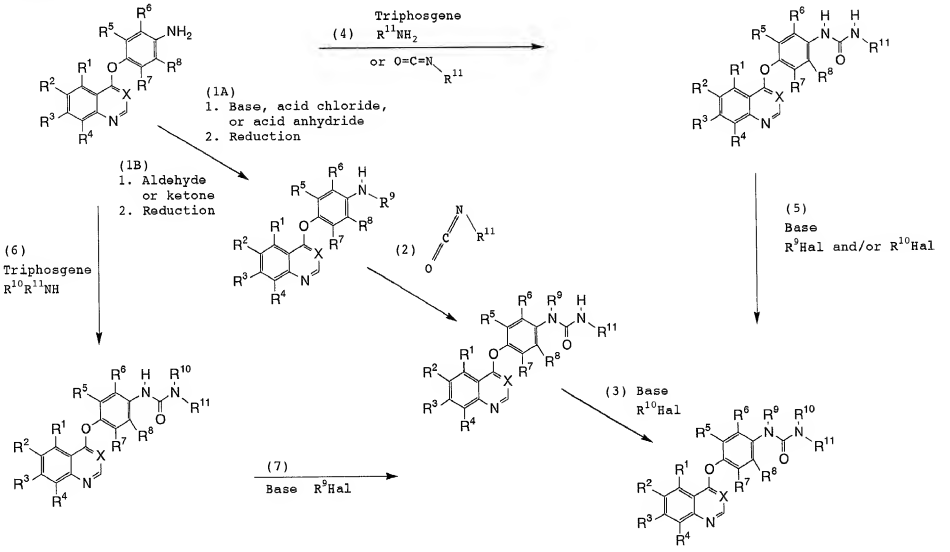
Alternatively, the 4-chloroquinazoline derivative may be produced by a process which comprises the steps of: (1) first reacting a benzoic ester with formamide to prepare a quinazolone derivative (see Production Example 34) and (2) then heating the 4-quinazolone derivative using toluene or sulfolane as a solvent in the presence of phosphorus oxychloride (see Production Examples 35 and 36). The quinazolone derivative is generally synthesized in the presence of a benzoic ester, sodium methoxide, formamide, and a solvent such as DMF or methanol. In the step (1), the reaction proceeds in a system where only the benzoic ester and formaldehyde are present. This is advantageous in that the synthesis can be carried out using a small number of starting compounds. The 4-quinazolone derivative is generally halogenated by heating the quinazolone derivative and phosphorus oxychloride. In this case, in many cases, due to high reactivity of the quinazoline derivative, the influence of the solvent has caused the quinazoline derivative to be returned to the starting compound and consequently made it impossible to complete the reaction. In the step (2), the reaction is completed in the presence of toluene or sulfolane, and, thus, this is advantageous from the viewpoint of an increase in yield.

Next, 4-chloroquinoline derivative or a corresponding quinazoline derivative is allowed to act

on nitrophenol in the presence of a suitable solvent or in the absence of a solvent to synthesize a 4-(nitrophenoxy)quinoline derivative or a corresponding quinazoline derivative which is then stirred in a suitable solvent, for example, N,N-dimethylformamide, in the presence of a catalyst, for example, palladium hydroxide-carbon or palladium-carbon, in a hydrogen atmosphere to give a 4-(aminophenoxy)quinoline derivative or a corresponding quinazoline derivative. Alternatively, a 4-chloroquinoline derivative or a corresponding quinazoline derivative may be allowed to act on aminophenol in the presence of a base, for example, sodium hydride, to give a 4-(aminophenoxy)quinoline derivative or a corresponding quinazoline derivative.

Alternatively, the 4-(aminophenoxy)quinoline derivative or the corresponding quinazoline derivative may also be produced by dissolving aminophenol in an aqueous sodium hydroxide solution and then subjecting the solution to a two-phase reaction with a solution of a 4-chloroquinazoline derivative or a corresponding quinazoline derivative in an organic solvent in the presence of a phase transfer catalyst or in the absence of a catalyst (see Production Examples 37 and 38). In this reaction, for example, phenol remaining unreacted and a decomposition product of 4-chloroquinazoline are left in the aqueous layer, while the target product is present in the organic layer. That is, the organic layer contains only the target product. Therefore, the post-treatment is advantageously simple. Further, the production of N-alkylaminophenoxy-quinazoline as a by-product can be advantageously suppressed.

Scheme 2



The 4-(aminophenoxy)quinoline derivative or the corresponding quinazoline derivative thus obtained may be reacted with an acid chloride or an acid anhydride in the presence of a base, followed by reduction, for example, with lithium aluminum hydride to introduce a substituent into R^9 (step 1A).

Alternatively, the 4-(aminophenoxy)quinoline derivative or the corresponding quinazoline derivative may be reacted with an aldehyde or a ketone to produce an imine, followed by reduction, for example, with sodiumboroncyanohydride to introduce a substituent into R^9 (step 1B).

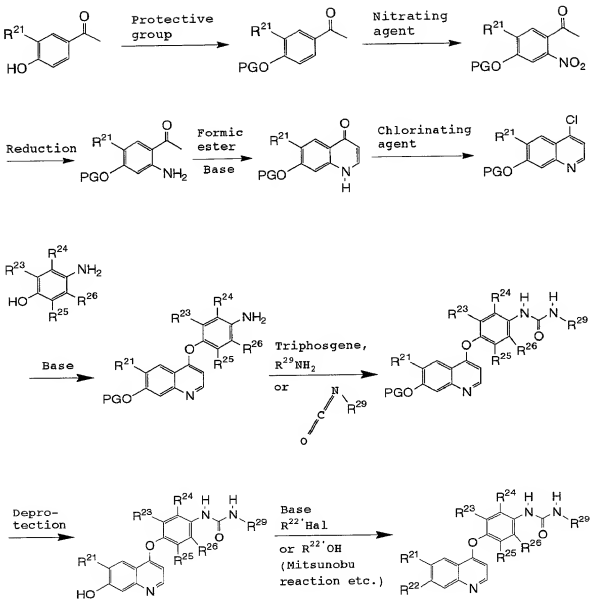
The derivative with a substituent introduced into R^9 is allowed to act on an isocyanate derivative ($O=C=N-R^{11}$) by a conventional method (step 2), and a suitable alkylating agent ($R^{10}Hal$) is allowed to act in the presence of a base, for example, sodium hydride (step 3) to produce the compound of formula (I).

Alternatively, R^9 and R^{10} may also be introduced by allowing a suitable alkylating agent (R^9Hal, $R^{10}Hal$) to act on a urea derivative, wherein R^9 and/or R^{10} represent a hydrogen atom, in the presence of a base, for example, sodium hydride (steps 5 and 7).

The urea derivative, wherein R^9 and/or R^{10} represent a hydrogen atom, may be produced by allowing an isocyanate derivative to act on the 4-(aminophenoxy)quinoline derivative or the corresponding quinazoline derivative, produced in scheme 1, according to a conventional method, or by adding a triphosgene to the 4-(aminophenoxy)quinoline derivative or the corresponding quinazoline derivative in the presence of a base, for example, triethylamine, and then reacting the mixture with a suitable alkylamine ($R^{11}NH_2$, $R^{10}R^{13}NH$) (steps 4 and 6).

The derivative having a specific substituent at the 7-position of the quinoline ring may be produced, for example, according to scheme 3.

Scheme 3



A suitable substituent (for example, benzyl) may be allowed to act on a commercially available 4'-hydroxyacetophenone derivative to protect the hydroxyl group, followed by action of a nitrating agent (for example, nitric acid-acetic acid) to introduce a nitro group.

The nitro group may be then reduced to an amino group which is then reacted with a formic ester in the

presence of a base to form a quinolone ring, followed by action of a chlorinating agent, for example, phosphorus oxychloride, to produce a 4-chloroquinoline derivative.

The 4-chloroquinoline derivative thus obtained may be allowed to act on aminophenol in the presence of a base, for example, sodium hydride, to produce a 4-(aminophenoxy)quinoline derivative.

The urea portion may be synthesized by allowing an isocyanate derivative ($O=C=N-R^{29}$) to act on the derivative thus obtained according to a conventional method, or by treating the derivative with triphosgene and then allowing an aromatic amine or alkylamine ($R^{29}NH_2$) to act on the treated derivative.

Next, the protective group (PG) for the hydroxyl group at the 7-position of the quinoline ring may be removed, followed by action of an alkyl halide ($R^{22'}Hal$ wherein $R^{22'}$ represents an alkyl portion when R^{22} represents alkoxy) in the presence of a base, or by action of an alcohol derivative ($R^{22'}OH$) according to a conventional method, for example, Mitsunobu reaction, to produce a compound, according to the present invention, having an alkoxy group at the 7-position of the quinoline ring.

The alkyl halide used in the substitution reaction may be commercially available or produced according to a process described, for example, in J. Am. Chem. Soc., 1945, 67, 736.

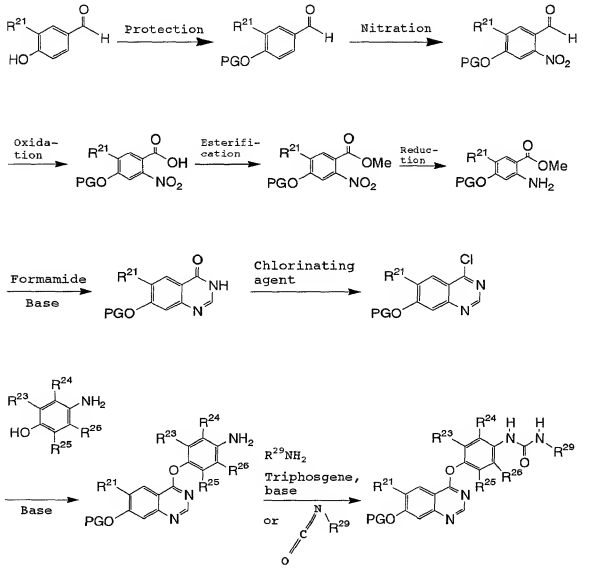
The alcohol derivative used in the substitution reaction may be commercially available or produced according to a process described, for example, in J. Antibiot. (1993), 46(1), 177 and Ann. Pharm. Fr. 1977, 35, 503.

The derivative having a specific substituent at the 6-position of the quinoline ring may be produced using 3'-hydroxyacetophenone derivative as the starting compound according to scheme 3.

The derivative having a specific substituent at the

7-position of the quinazoline ring may be produced according to scheme 4.

Scheme 4



The 2-amino-benzoic ester derivative may be produced by esterifying a 2-nitro-benzoic acid derivative synthesized according to a method described, for example, in J. Med. Chem. 1977, 20, 146, for example, with dimethylsulfuric acid in the presence of a base, for example, potassium carbonate and then reducing the nitro group, for example, with iron/acetic acid.

Next, the compound thus obtained may be allowed to act on formamide in the presence of a base to form a 4-quinazolone ring, followed by action of a chlorinating agent, for example, phosphorus oxychloride, to produce a 4-chloroquinazoline derivative.

The 4-chloroquinazoline derivative thus obtained may be allowed to act on an aminophenol derivative in the presence of a base, for example, sodium hydride, to produce a 4-(aminophenoxy)quinazoline derivative.

The urea portion may be synthesized by allowing an isocyanate derivative ($O=C=N-R^{29}$) to act on the derivative thus obtained according to a conventional method, or by treating the derivative with triphosgene and then allowing an aromatic amine or alkylamine ($R^{29}NH_2$) to act on the treated derivative.

Next, the protective group (PG) for the hydroxyl group at the 7-position of the quinazoline ring may be removed, followed by action of an alkyl halide ($R^{22'}Hal$ wherein $R^{22'}$ represents an alkyl portion when R^{22} represents alkoxy) in the presence of a base, or by action of an alcohol derivative ($R^{22'}OH$) according to a conventional method, for example, Mitsunobu reaction, to produce a compound, according to the present invention, having an alkoxy group at the 7-position of the quinazoline ring.

The alkyl halide and the alcohol derivative used in the substitution reaction may be commercially available or produced according to a process described in the literature referred to in the description of scheme 3.

The derivative having a specific substituent at the

6-position of the quinazoline ring may be produced using 3-hydroxybenzaldehyde derivative as the starting compound according to scheme 4.

Use of compounds/pharmaceutical composition

The compounds according to the present invention have inhibitory activity against tumor proliferation in vivo (see Pharmacological Test Example 4).

Further, the compounds according to the present invention inhibit in vitro the activation of MAPK (mitogen-activated protein kinase) caused by stimulation of vascular endothelial cells with VEGF (vascular endothelial growth factor) (see Pharmacological Test Examples 1 and 2). Upon the stimulation of vascular endothelial cells with VEGF, MAPK is activated by a signal transmission system downstream of the receptor, and, consequently, an increase in phosphorylated MAPK is recognized (Abedi, H. and Zachary, I., J. Biol. Chem., 272, 15442-15451 (1997)). The activation of MAPK is known to play an important role in the growth of vascular endothelial cells in angiogenesis (Merenmies, J. et al., Cell Growth & Differ., 83-10 (1997); and Ferrara, N. and Davis-Smyth, T., Endocr. Rev., 18, 4-25 (1997)). Therefore, the compounds according to the present invention have angiogenesis inhibitory activity.

Angiogenesis at pathologic sites is deeply involved mainly in diseases, such as tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, and metastasis of solid tumors (Forkman, J. Nature Med. 1: 27-31 (1995); Bicknell, R., Harris, A. L. Curr. Opin. Oncol. 8: 60-65 (1996)). Therefore, the compounds according to the present invention can be used in the treatment of diseases, such as tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, and metastasis of solid tumors.

The compounds according to the present invention have no significant influence on cytomorphosis (see

Pharmacological Test Example 3). Therefore, the compounds according to the present invention can be administered to living bodies with very excellent safety.

According to the present invention, there is provided a pharmaceutical composition comprising the compound according to the present invention. The pharmaceutical composition according to the present invention may be used in the treatment of diseases, such as tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, and metastasis of solid tumors.

Further, according to the present invention, there is provided a method for treating a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, comprising the step of administering the compound according to the present invention, together with a pharmaceutically acceptable carrier, to mammals.

The compounds according to the present invention can be administered to human and non-human animals orally or parenterally by administration routes, for example, intravenous administration, intramuscular administration, subcutaneous administration, rectal administration, or percutaneous administration. Therefore, the pharmaceutical composition comprising as an active ingredient the compound according to the present invention is formulated into suitable dosage forms according to the administration routes.

Specifically, oral preparations include tablets, capsules, powders, granules, and syrups, and parental preparations include injections, suppositories, tapes, and ointments.

These various preparations may be prepared by conventional methods, for example, with commonly used component, such as excipients, disintegrants, binders, lubricants, colorants, and diluents.

Excipients include, for example, lactose, glucose, corn starch, sorbit, and crystalline cellulose. Disintegrants include, for example, starch, sodium alginate, gelatin powder, calcium carbonate, calcium citrate, and dextrin. Binders include, for example, dimethylcellulose, polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, gelatin, hydroxypropylcellulose, and polyvinyl pyrrolidone. Lubricants include, for example, talc, magnesium stearate, polyethylene glycol, and hydrogenated vegetable oils.

In preparing injections, if necessary, for example, buffers, pH adjustors, stabilizers, tonicity agents, and preservatives may be added.

The content of the compound according to the present invention in the pharmaceutical composition according to the present invention may vary according to the dosage form. In general, however, the content is 0.5 to 50% by weight, preferably 1 to 20% by weight, based on the whole composition.

The dose may be appropriately determined in consideration of, for example, the age, weight, sex, difference in diseases, and severity of condition of patients, and the preparation may be administered, for example, in an amount of 0.1 to 100 mg/kg, preferably 1 to 50 mg/kg. This dose is administered at a time daily or divided doses of several times daily.

The compound according to the present invention may be administered in combination with other medicament(s). In this case, the compound according to the present invention may be administered simultaneously with or after or before the administration of other medicament(s). For example, when the object disease is malignant tumor, the compound according to the present invention can be allowed to act on target vascular endothelial cells to allow the tumor to regress, followed by the administration of a carcinostatic agent

to effectively eliminate the tumor. The type, administration intervals and the like of the carcinostatic agent may be determined depending upon, for example, the type of cancer and the condition of patients. This treatment method is true of diseases other than the malignant tumor.

Furthermore, according to the present invention, there is provided a method for inhibiting the angiogenesis of target blood vessels, comprising the step of making the compound according to the present invention in contact with vascular endothelial cells of target blood vessels. Target blood vessels include blood vessels involved in feedings to tissues causative of diseases (for example, tumor tissues, retinopathy tissues, or rheumatism tissues). The compound according to the present invention may be brought into contact with the vascular endothelial cells, for example, by general administration (for example, intravenous administration or oral administration), local administration (for example, percutaneous administration or intraarticular administration), or drug targeting using a carrier (for example, liposome, lipid microsphere, or polymeric forms of drugs).

EXAMPLES

The present invention will be described with reference to the following examples, though it is not limited to these examples only.

Production Example 1: 2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline

Sodium hydride (60 wt%, 0.72 g) was added to dimethyl sulfoxide (10 ml). The mixture was stirred at 50°C for 30 min and was then cooled to room temperature. 4-Amino-3-chlorophenol hydrochloride (1.61 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6,7-dimethoxyquinoline (1.00 g) was added thereto, and the

mixture was stirred at 100°C overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue. The precipitated crystal was collected by suction filtration to give 0.89 g (yield 60%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.05 (s, 3H), 4.08 (s, 2H), 6.44 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.93 - 6.96 (m, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.41 (s, 1H), 7.54 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Production Example 2: 4-[(6,7-Dimethoxy-4-quinolyl)oxyl-2,3-dimethylaniline

Sodium hydride (60 wt%, 0.72 g) was added to dimethyl sulfoxide (10 ml). The mixture was stirred at 50°C for 30 min and was then cooled to room temperature. 4-Amino-2,3-dimethylphenol hydrochloride (1.55 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6,7-dimethoxyquinoline (1.00 g) was added thereto, and the mixture was stirred at 100°C overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue. The precipitated crystal was collected by suction filtration to give 0.94 g (yield 65%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 3H), 2.15 (s, 3H), 3.62 (s, 2H), 4.05 (s, 3H), 4.07 (s, 3H), 6.25 (d, J = 5.4 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.64 (s, 1H), 8.42 (d, J = 5.4 Hz, 1H)

Production Example 3: 4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline

Sodium hydride (60 wt%, 0.36 g) was added to dimethyl sulfoxide (10 ml), and the mixture was stirred at 50°C for 30 min and was then cooled to room temperature. 4-Amino-2,5-dimethylphenol (1.23 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6,7-dimethoxyquinoline (1.00 g) was added thereto, and the mixture was stirred at 100°C overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (1/1) to give the title compound.

Production Example 4: 3,5-Dichloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline

Sodium hydride (60 wt%, 0.36 g) was added to dimethyl sulfoxide (10 ml), and the mixture was stirred at 50°C for 30 min and was then cooled to room temperature. 4-Amino-2,6-dichlorophenol (1.59 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6,7-dimethoxyquinoline (1.00 g) was added thereto, and the mixture was stirred at 100°C overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (1/1) to give 0.35 g (yield 22%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.84 (s, 2H), 4.05 (s,

3H), 4.08 (s, 3H), 6.28 (d, J = 5.4 Hz, 1H), 6.74 (s, 2H), 7.43 (s, 1H), 7.64 (s, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Production Example 5: 4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-nitroaniline

Sodium hydride (60 wt%, 0.54 g) was added to dimethyl sulfoxide (15 ml), and the mixture was stirred at 70°C for 30 min and was then cooled to room temperature. 4-Amino-3-nitrophenol (2.07 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6,7-dimethoxyquinoline (1.50 g) was added thereto, and the mixture was stirred at 100°C for 4 hr. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (1/1) to give 0.53 g (yield 23%) of the title compound.

Production Example 6: 1-[2-Amino-4-(benzyloxy)-5-methoxyphenyl]-1-ethanone

1-(4-Hydroxy-3-methoxyphenyl)-1-ethanone (20 g), potassium carbonate (18.3 g), tetra-n-butylammonium iodide (4.45 g), and benzyl bromide (17.3 ml) were dissolved in N,N-dimethylformamide (300 ml), and a reaction was allowed to proceed at 100°C for one hr. The solvent was removed by distillation under the reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate. Next, the solvent was removed by distillation under the reduced pressure. The residue and fuming nitric acid (12.47 ml) were dissolved in acetic acid (120 ml), and a reaction was allowed to proceed at room temperature for 2 hr. The reaction solution was neutralized at 0°C by the addition

of an aqueous sodium hydroxide solution, followed by extraction with chloroform. The chloroform layer was then dried over sodium sulfate. Next, the solvent was removed by distillation under the reduced pressure. The residue was dissolved in ethanol (1160 ml) and water (120 ml) with heating. Ammonium chloride (19.2 g) and zinc (101.7 g) were added thereto. The mixture was heated under reflux for 3 hr. The reaction solution was filtered through Celite, followed by washing with chloroform/methanol (3/1). The solvent was removed by distillation under the reduced pressure, and the residue was made alkaline with an aqueous sodium hydroxide solution, and the alkaline solution was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/ethyl acetate (10/1) to give 24.95 g (yield 77%) of the title compound (3 steps).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.51 (s, 3H), 3.84 (s, 3H), 5.14 (s, 2H), 6.12 (s, 2H), 7.15 - 7.62 (m, 7H)

Production Example 7: 7-(Benzyloxy)-6-methoxy-1,4-dihydro-4-quinolinone

1-[2-Amino-4-(benzyloxy)-5-methoxyphenyl]-1-ethanone (24.95 g) was dissolved in tetrahydrofuran (450 ml), and sodium methoxide (24.87 g) was added to the solution. The mixture was stirred at room temperature for one hr. Ethyl formate (37.07 ml) was then added thereto, and the mixture was stirred at room temperature for 2 hr. Water (150 ml) was then added thereto, and the mixture was stirred overnight. The reaction solution was adjusted to pH 4 by the addition of concentrated sulfuric acid at 0°C. Water was added thereto, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by

development with chloroform/methanol (10/1) to give 17.16 g (yield 66%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.84 (s, 3H), 5.19 (s, 2H), 5.97 (d, J = 7.1 Hz, 1H), 7.09 (s, 1H), 7.28 - 7.51 (m, 6H), 7.78 (d, J = 7.3 Hz, 1H), 11.50 - 11.75 (br, 1H)

Production Example 8: 7-(Benzyloxy)-4-chloro-6-methoxyquinoline

Phosphorus oxychloride (14.19 ml) was added to 7-(benzyloxy)-6-methoxy-1,4-dihydro-4-quinolinone (17.16 g), and the mixture was heated under reflux for one hr. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in chloroform, and the solution was made alkaline by the addition of an aqueous sodium hydroxide solution, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (10/1) to give 3.82 g (yield 21%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.06 (s, 3H), 5.32 (s, 2H), 7.30 - 7.55 (m, 8H), 8.56 (d, J = 4.9 Hz, 1H)

Production Example 9: 4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylaniline

Sodium hydride (60 wt%, 1.17 g) was added to dimethyl sulfoxide (25 ml), and the mixture was stirred at 60°C for 30 min and was then cooled to room temperature. Next, 4-amino-2,5-dimethylphenol (4.00 g) was added thereto, and the mixture was stirred at room temperature for 10 min. 7-(Benzyloxy)-4-chloro-6-methoxyquinoline (4.36 g) was then added thereto. The mixture was stirred for 22 hr before water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was

removed by distillation under the reduced pressure, and methanol was added to the residue to prepare a suspension. The precipitated crystal was collected by suction filtration to give 3.04 g (yield 52%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.05 (s, 3H), 2.16 (s, 3H), 3.58 (s, 2H), 4.06 (s, 3H), 5.32 (s, 2H), 6.28 (d, J = 5.1 Hz, 1H), 6.61 (s, 1H), 6.81 (s, 1H), 7.28 - 7.42 (m, 3H), 7.44 (s, 1H), 7.49 - 7.54 (m, 2H), 7.63 (s, 1H), 8.39 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 401 (M^++1)

Production Example 10: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2,4-difluorophenyl)urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylaniline (300 mg) was dissolved in chloroform (5 ml). 2,4-Difluorophenyl isocyanate (200 µl) was then added to the solution, and the mixture was stirred at 70°C overnight. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (75/25) to give 368 mg (yield 88%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.26 (s, 3H), 4.06 (s, 3H), 5.33 (s, 2H), 6.29 (d, J = 5.1 Hz, 1H), 6.42 (s, 1H), 6.76 - 6.93 (m, 3H), 6.70 (s, 3H), 7.30 - 7.54 (m, 7H), 7.60 (s, 1H), 8.04 - 8.12 (m, 1H), 8.44 (d, J = 5.4 Hz, 1H)

Production Example 11: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2-methoxyphenyl)-urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylaniline (300 mg) was dissolved in chloroform (5 ml). 2-Methoxyphenyl isocyanate (0.24 ml) was then added to the solution, and the mixture was stirred at 70°C overnight. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (75/25) to give 365 mg (yield 89%) of

the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.28 (s, 3H), 3.83 (s, 3H), 4.07 (s, 3H), 5.33 (s, 2H), 6.26 (s, 3H), 6.29 (d, J = 5.4 Hz, 1H), 6.86 - 7.06 (m, 4H), 7.12 (s, 1H), 7.30 - 7.41 (m, 3H), 7.46 (s, 1H), 7.50 - 7.56 (m, 3H), 7.61 (s, 1H), 8.11 - 8.16 (m, 1H), 8.43 (d, J = 5.4 Hz, 1H)

Production Example 12: 4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-chloroaniline

Sodium hydride (60 wt%, 320 mg) was added to dimethyl sulfoxide (3.6 ml), and the mixture was stirred at 60°C for 30 min and was then cooled to room temperature. Next, 4-amino-3-chlorophenol hydrochloride (720 mg) was added thereto, and the mixture was stirred at room temperature for 10 min. 7-(Benzyloxy)-4-chloro-6-methoxyquinoline (600 mg) was then added thereto, and the mixture was stirred at 105°C for 22 hr. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue to prepare a suspension. The precipitated crystal was collected by suction filtration to give 533 mg (yield 66%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.08 (s, 2H), 5.32 (s, 2H), 6.42 (d, J = 5.1 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.93 (dd, J = 2.4 Hz, 8.1 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.29 - 7.42 (m, 3H), 7.44 (s, 1H), 7.49 - 7.53 (m, 2H), 7.55 (s, 1H), 8.45 (d, J = 5.3 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 497 (M^++1)

Production Example 13: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)-urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-

chloroaniline (260 mg) was dissolved in chloroform (10 ml). 2,4-Difluorophenyl isocyanate (198 mg) was then added to the solution, and the mixture was stirred at room temperature for 2 hr. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (10/1) to give 337 mg (yield 94%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.04 (s, 3H), 5.32 (s, 2H), 6.49 (d, J = 5.1 Hz, 1H), 6.86 - 6.96 (m, 3H), 7.10 - 7.17 (m, 2H), 7.22 - 7.28 (m, 1H), 7.28 - 7.41 (m, 3H), 7.45 - 7.53 (m, 4H), 7.96 - 8.04 (m, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 562, 564 (M^++1)

Production Example 14: N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-(2,4-difluorophenyl)-urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea (215 mg) was dissolved in dimethylformamide (11 ml). Palladium-carbon (215 mg) was added to the solution, and the mixture was stirred in a hydrogen atmosphere at room temperature overnight. Ethyl acetate (30 ml) was added to the reaction solution, and the mixture was then filtered through Celite. The solvent was removed by distillation under the reduced pressure to give 174 mg (yield 96%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.94 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.01 - 7.11 (m, 1H), 7.18 - 7.36 (m, 3H), 7.44 - 7.52 (m, 2H), 7.95 (s, 1H), 7.98 - 8.13 (m, 1H), 8.23 (d, J = 9.5 Hz, 1H), 6.50 (d, J = 5.1 Hz, 1H), 8.81 (s, 1H), 9.31 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 472 (M^++1)

Production Example 15: 4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,3-dimethylaniline

Sodium hydride (60 wt%, 0.32 g) was added to dimethyl sulfoxide (6 ml), and the mixture was stirred at room temperature for 30 min. 4-Amino-2,3-

dimethylphenol (1.10 g) was then added thereto, and the mixture was stirred at room temperature for 10 min. Next, 7-(benzyloxy)-4-chloro-6-methoxyquinoline (1.20 g) was added thereto, and the mixture was stirred at 110°C for 6 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (6/1) to give 0.78 g (yield 49%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.87 (s, 3H), 1.96 (s, 3H), 3.97 (s, 3H), 4.78 (s, 2H), 5.23 (s, 2H), 6.12 (d, J = 5.3 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 7.27 - 7.51 (m, 7H), 8.31 (d, J = 5.3 Hz, 1H)

Production Example 16: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,3-dimethylphenyl)-N'-(2,4-difluorophenyl)urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,3-dimethylaniline (260 mg) was dissolved in N,N-dimethylformamide (5 ml). 2,4-Difluorophenyl isocyanate (121 mg) was then added to the solution, and a reaction was allowed to proceed at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was washed with methanol and was collected by filtration to give 219 mg (yield 61%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.99 (s, 3H), 2.17 (s, 3H), 3.90 (s, 3H), 5.24 (s, 2H), 6.18 (d, J = 5.1 Hz, 1H), 6.95 - 6.98 (m, 2H), 7.25 - 7.63 (m, 9H), 8.05 - 8.08 (m, 1H), 8.34 - 8.36 (m, 2H), 8.79 (s, 1H)

Production Example 17: 7-(Benzyloxy)-4-(3-fluoro-4-nitrophenoxy)-6-methoxyquinoline

7-(Benzyloxy)-4-chloro-6-methoxyquinoline (300 mg)

and 3-fluoro-4-nitrophenol (785 mg) were dissolved in chlorobenzene (3 ml), and the solution was stirred at 130°C for 5 hr. Chloroform and an aqueous sodium hydroxide solution were added to the reaction solution, and the mixture was stirred for one hr. The reaction solution was extracted with chloroform, and the chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with hexane/ethyl acetate (1/1) to give 197 mg (yield 47%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.83 (s, 3H), 5.25 (s, 2H), 6.91 (d, J = 5.1 Hz, 1H), 7.29 - 7.50 (m, 9H), 8.18 - 8.23 (m, 1H), 8.56 (d, J = 5.1 Hz, 1H)

Production Example 18: 4-(4-Amino-3-fluorophenoxy)-6-methoxy-7-quinolinol

7-(Benzyloxy)-4-(3-fluoro-4-nitrophenoxy)-6-methoxyquinoline (190 mg) was dissolved in N,N-dimethylformamide (5 ml) and triethylamine (1 ml). Palladium hydroxide (40 mg) was added to the solution, and the mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (20/1) to give 75 mg (yield 56%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.87 (s, 3H), 5.11 (s, 2H), 6.29 (d, J = 5.1 Hz, 1H), 6.77 - 6.80 (m, 2H), 6.93 - 6.99 (m, 1H), 7.19 (s, 1H), 7.40 (s, 1H), 8.31 (d, J = 5.1 Hz, 1H), 10.03 (s, 1H)

Production Example 19: N-(2,4-Difluorophenyl)-N'-{2-fluoro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-urea

4-(4-Amino-3-fluorophenoxy)-6-methoxy-7-quinolinol (70 mg) was dissolved in chloroform (1.5 ml) and N,N-dimethylformamide (1 ml). 2,4-Difluorophenyl isocyanate

(43 mg) was then added to the solution, and a reaction was allowed to proceed at room temperature for 3 hr. Methanol was added to the reaction solution. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (20/1) to quantitatively give the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.94 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.04 - 7.10 (m, 2H), 7.28 - 7.34 (m, 2H), 7.47 (s, 1H), 8.05 - 8.15 (m, 2H), 8.30 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.97 - 9.03 (m, 2H), 10.10 (s, 1H)

Production Example 20: 4-Chloro-6-methoxy-7-quinolinol

7-(Benzyloxy)-4-chloro-6-methoxyquinoline (100 mg), thioanisole (300 μl), and methanesulfonic acid (25 μl) were dissolved in trifluoromethanesulfonic acid (1 ml). The solution was stirred at room temperature for 30 min. The solvent was removed by distillation under the reduced pressure. The residue was made neutral by the addition of an aqueous sodium hydroxide solution, and hexane was added thereto to prepare a suspension. The crystal was collected by suction filtration to give 53 mg (yield 75%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 7.33 (s, 1H), 7.36 (s, 1H), 7.47 (d, J = 4.9 Hz, 1H), 8.54 (d, J = 4.9 Hz, 1H), 10.37 (br, 1H)

Production Example 21: 4-Chloro-6-methoxy-7-(2-methoxyethoxy)quinoline

4-Chloro-6-methoxy-7-quinolinol (50 mg), potassium carbonate (40 mg), tetra-n-butylammonium iodide (9 mg), and 2-bromoethyl methyl ether (40 mg) were dissolved in N,N-dimethylformamide (10 ml). The solution was stirred at 70°C overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The

solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with hexane/acetone/dichloromethane (6/2/1) to give 47 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.49 (s, 3H), 3.88 - 3.90 (m, 2H), 4.04 (s, 3H), 4.32 - 4.35 (m, 2H), 7.35 (d, J = 4.9 Hz, 1H), 7.40 (s, 1H), 7.43 (s, 1H), 8.57 (d, J = 4.9 Hz, 1H)

Production Example 22: 2-Chloro-4-{[(6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}aniline

Sodium hydride (60 wt%, 153 mg) was added to dimethyl sulfoxide (2 ml). The mixture was stirred at 60°C for 30 min and was then cooled to room temperature. 4-Amino-3-chlorophenol hydrochloride (343 mg) was added thereto, and the mixture was stirred at room temperature for 10 min. Next, a solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline (254 mg) in dimethyl sulfoxide (2 ml) was added to the reaction solution, and the mixture was stirred at 110°C overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (7/3) to give the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.49 (s, 3H), 3.89 - 3.91 (m, 2H), 4.02 (s, 3H), 4.09 (s, 2H), 4.33 - 4.35 (m, 2H), 6.43 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.93 - 6.96 (m, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.41 (s, 1H), 7.52 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H)

Production Example 23: 2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]aniline

Sodium hydride (60 wt%, 5.80 g) was added to dimethyl sulfoxide (40 ml). The mixture was stirred at

60°C for 30 min and was then cooled to room temperature. Next, 4-amino-3-chlorophenol hydrochloride (13.05 g) was added thereto. The mixture was stirred at room temperature for 10 min. 4-Chloro-6,7-dimethoxyquinazoline (8.14 g), which is a chloroquinazoline derivative synthesized by a conventional method as described, for example, in J. Am. Chem. Soc., 68, 1299 (1946) or J. Am. Chem. Soc., 68, 1305 (1946), was then added thereto. The mixture was stirred at 110°C for 30 min. Water was then added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue to prepare a suspension. The precipitated crystal was collected by suction filtration to give 9.13 g (yield 76%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 - 4.08 (m, 8H), 6.85 (d, J = 8.5 Hz, 1H), 7.00 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.32 (s, 1H), 7.52 (s, 1H), 8.64 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 332 (M^++1)

Production Example 24: N-Benzyl-N-(2,4-difluorophenyl)amine

Magnesium sulfate (5.59 g) and a minor amount of acetic acid were added to a solution of 2,4-difluoroaniline (2.37 ml) and benzaldehyde (2.36 ml) in methanol (46 ml). The mixture was stirred at room temperature for 45 min. Sodium boron hydride (2.64 g) was added thereto under ice cooling, and the mixture was stirred at room temperature for one hr. The solvent was removed by distillation under the reduced pressure. Water and ethyl acetate were added to the residue. The mixture was stirred and was filtered through Celite. The organic layer was extracted with ethyl acetate and was

dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with hexane/acetone (30/1) to give 3.04 g (yield 60%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.34 (s, 2H), 6.56 - 6.82 (m, 3H), 7.25 - 7.38 (m, 5H)

Production Example 25: Methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate

Commercially available methyl vanillate (50 g) and potassium carbonate (76 g) were dissolved in N,N-dimethylformamide (200 ml). Benzyl bromide (33 ml) was added dropwise to the solution over a period of 10 min. The mixture was stirred at room temperature overnight. Water (200 ml) was added thereto, followed by extraction with ethyl acetate. Saturated brine was then added to the organic layer, and the mixture was extracted with ethyl acetate. Sodium sulfate was added to the organic layer to dry the organic layer. Next, the organic layer was filtered, and the solvent was then removed by distillation under the reduced pressure. The residue was dried through a vacuum pump to give 68 g of a white solid. Subsequently, 100 ml of acetic acid and 200 ml of nitric acid were added under ice cooling. The mixture was stirred for 8 hr, and water was then added thereto. The resultant solid was then collected by filtration, was thoroughly washed with water, and was dried through a vacuum pump to give 74 g (yield 93%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.90 (s, 3H), 3.98 (s, 3H), 5.21 (s, 2H), 7.08 (s, 1H), 7.31 - 7.45 (m, 5H), 7.51 (s, 1H)

Production Example 26: 7-(Benzyloxy)-6-methoxy-3,4-dihydro-4-quinazolinone

Methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate (15.0 g) was dissolved in acetic acid (200 ml) at room temperature. Iron (powder) (13.2 g) was then added to

the solution. The temperature of the mixture was raised to 90°C, and the mixture was then stirred for one hr. The resultant gray solid was filtered through Celite, followed by washing with acetic acid. Concentrated hydrochloric acid was added to the mother liquor. The solvent was then removed by distillation under the reduced pressure. This resulted in the precipitation of a solid. The solid was collected by filtration, was washed with ethyl acetate and ether, and was dried through a vacuum pump. Subsequently, chloroform and methanol were added to the solid to prepare a suspension, and a 10% aqueous sodium hydroxide solution was then added to dissolve the solid, followed by extraction with chloroform. After washing with water, the organic layer was dried over sodium sulfate. Next, the organic layer was filtered, and the solvent was then removed by distillation under the reduced pressure. The residue was dried through a vacuum pump to give 9.5 g (yield 70%) of a crude product of methyl 2-amino-4-(benzyloxy)-5-methoxybenzoate.

Methyl 2-amino-4-(benzyloxy)-5-methoxybenzoate (650 mg) was dissolved in N,N-dimethylformamide (15 ml) and methanol (3 ml). Formamide (0.46 ml) and sodium methoxide (373 mg) were added to the solution. The mixture was heated to 100°C and was stirred overnight. The reaction solution was cooled to room temperature, and 10 ml of water was then added to the cooled reaction solution. The reaction solution was neutralized with a 1 M aqueous hydrochloric acid solution to precipitate a solid. The solid was collected by filtration, was washed with water and ether, and was then dried through a vacuum pump to give 566 mg (yield 87%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.88 (s, 3H), 5.25 (s, 2H), 7.23 (s, 1H), 7.33 - 7.49 (m, 6H), 7.97 (s, 1H), 12.06 (br, 1H)

Production Example 27: 7-(Benzyloxy)-4-chloro-6-

methoxyquinazoline

Phosphorus oxychloride (515 ml) was added to 7-(benzyloxy)-6-methoxy-3,4-dihydro-4-quinazolinone (400 mg) and diisopropylethylamine (0.3 ml), and the mixture was refluxed for 20 min. The reaction solution was cooled to room temperature. A 10% aqueous sodium hydroxide solution was then added to the reaction solution, followed by extraction with chloroform. The organic layer was dried over sodium sulfate. The organic layer was filtered, and the solvent was then removed by distillation under the reduced pressure. The residue was dried through a vacuum pump to give 420 mg (yield 99%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.08 (s, 3H), 5.34 (s, 2H), 7.35 - 7.51 (m, 7H), 8.86 (s, 1H)

Production Example 28: Methyl 5-(benzyloxy)-4-methoxy-2-nitrobenzoate

Commercially available methyl 3-hydroxy-4-methoxybenzoate (10 g) and potassium carbonate (23 g) were dissolved in N,N-dimethylformamide (50 ml). Benzyl bromide (6.5 ml) was added dropwise to the solution over a period of 10 min. The mixture was stirred at room temperature overnight. Water (200 ml) was added thereto, and the mixture was extracted with ethyl acetate. Saturated brine was then added to the organic layer, followed by extraction with ethyl acetate. Sodium sulfate was added to the organic layer to dry the organic layer. Next, the organic layer was filtered, and the solvent was then removed by distillation under the reduced pressure. The residue was dried through a vacuum pump to give 8.4 g of a white solid. Subsequently, 7.0 g of the solid was placed in a flask, and 100 ml of acetic acid and 200 ml of nitric acid were added thereto under ice cooling. The mixture was stirred for 8 hr, and water was then added thereto. The resultant solid was collected by filtration, was thoroughly washed with water, and was dried through a vacuum pump to give 7.9 g

(yield 96%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.89 (s, 3H), 3.96 (s, 3H), 5.21 (s, 2H), 7.15 (s, 1H), 7.34 - 7.45 (m, 6H)

Production Example 29: 6-(Benzyloxy)-7-methoxy-3,4-dihydro-4-quinazolinone

Methyl 5-(benzyloxy)-4-methoxy-2-nitrobenzoate (15.8 g) was dissolved in acetic acid (200 ml) at room temperature. Iron (powder) (13.9 g) was then added to the solution. The mixture was heated to 90°C and was stirred for one hr. The resultant gray solid was filtered through Celite and was washed with acetic acid. Concentrated hydrochloric acid was added to the mother liquor, and the solvent was then removed by distillation under the reduced pressure to precipitate a solid. The solid was collected by filtration, was washed with ethyl acetate and ether, and was dried through a vacuum pump. Subsequently, chloroform and methanol were added to the solid to prepare a suspension, and a 10% aqueous sodium hydroxide solution was then added to the suspension to dissolve the solid, followed by extraction with chloroform. The extract was washed with water, and the organic layer was then dried over sodium sulfate. Next, the organic layer was filtered, and the solvent was then removed by distillation under the reduced pressure. The residue was dried through a vacuum pump to give 10.4 g (yield 73%) of a crude product of methyl 2-amino-5-(benzyloxy)-4-methoxybenzoate.

Methyl 2-amino-5-(benzyloxy)-4-methoxybenzoate (5.0 g) was dissolved in N,N-dimethylformamide (150 ml) and methanol (30 ml). Formamide (3.5 ml) and sodium methoxide (2.8 g) were added to the solution. The mixture was heated to 100°C and was then stirred overnight. The reaction solution was then cooled to room temperature, and 10 ml of water was then added. The reaction solution was neutralized with a 1 M aqueous hydrochloric acid solution to precipitate a solid. The solid was collected by filtration, was washed with water

and ether, and was then dried through a vacuum pump to give 3.7 g (yield 76%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.92 (s, 3H), 5.21 (s, 2H), 7.16 (s, 1H), 7.33 - 7.49 (m, 5H), 7.55 (s, 1H), 7.99 (s, 1H), 12.06 (br, 1H)

Production Example 30: 6-(Benzyloxy)-4-chloro-7-methoxyquinazoline

Phosphorus oxychloride (3.1 ml) was added to 6-(benzyloxy)-7-methoxy-3,4-dihydro-4-quinazolinone (3.5 g) and diisopropylethylamine (11.5 ml). The mixture was refluxed for 20 min. The reaction solution was cooled to room temperature, and a 10% aqueous sodium hydroxide solution was then added to the cooled reaction solution, followed by extraction with chloroform. The organic layer was dried over sodium sulfate. The organic layer was filtered, and the solvent was then removed by distillation under the reduced pressure. The residue was dried through a vacuum pump to give 2.9 g (yield 72%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.07 (s, 3H), 5.32 (s, 2H), 7.35 - 7.53 (m, 7H), 8.86 (s, 1H)

Production Example 31: 4-{[7-(Benzyloxy)-6-methoxy-4-quinazolinyl]oxy}-2-chloroaniline

7-(Benzyloxy)-4-chloro-6-methoxyquinazoline (30.0 g) and tetrabutylammonium chloride (13.9 g) were dissolved in acetone (400 ml), and the solution was stirred at room temperature. A solution of 4-amino-3-chlorophenol hydrochloride (36.0 g) in a 20% aqueous sodium hydroxide solution (64 ml) was added thereto. The mixture was then heated under reflux for 3 hr. The reaction solution was cooled to room temperature, and chloroform and water were added to the cooled reaction solution, followed by extraction with chloroform. The extract was washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine and was then dried over anhydrous sodium sulfate. Next, sodium sulfate was removed, and the solvent was then removed by

distillation. The residue was washed with methanol, and the washed solid was subjected to evaporation to dryness in vacuo through a vacuum pump to give 36.6 g (yield 90%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.96 (s, 3H), 5.34 (s, 2H), 6.86 (d, J = 8.8 Hz, 1H), 7.00 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.35 - 7.54 (m, 7H), 8.53 (s, 1H)

Production Example 32: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propylurea

4-{[7-(Benzyloxy)-6-methoxy-4-quinazolinyl]oxy}-2-chloroaniline (12.2 g) was dissolved in anhydrous chloroform. Triethylamine (8.4 ml) was then added to the solution, and the mixture was stirred at room temperature. Separately, triphosgene (4.5 g) was dissolved in anhydrous chloroform (12 ml), and the solution was added dropwise to the mixed solution. The mixture was stirred at room temperature for 20 min, and n-propylamine (4.9 ml) was then added thereto, followed by stirring at room temperature for additional one hr to precipitate a white solid. This solid was collected by filtration and was then washed with chloroform to give 9.4 g (yield 63%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.44 - 1.50 (m, 2H), 3.06 - 3.09 (m, 2H), 3.98 (s, 3H), 5.35 (s, 2H), 6.97 - 7.01 (m, 1H), 7.23 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.37 - 7.57 (m, 9H), 8.20 (d, J = 9.3 Hz, 1H), 8.55 (s, 1H)

Production Example 33: N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propylurea (42.2 g) was dissolved in trifluoroacetic acid (200 ml). Methanesulfonic acid (11.1 ml) was then added to the solution, and the mixture was stirred at 100°C for 4 hr. The reaction solution was cooled to room temperature, and trifluoroacetic acid was removed by distillation under

the reduced pressure. Chloroform and methanol were added to the mixture as the residue, followed by extraction with a 10% aqueous sodium hydroxide solution three times. The aqueous layer was neutralized with concentrated hydrochloric acid to precipitate a solid. The solid was washed with water, methanol, and ether in that order, and was then dried in vacuo through a vacuum pump to give 20.7 g (yield 60%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.42 - 1.49 (m, 2H), 3.06 - 3.17 (m, 2H), 3.84 (s, 3H), 6.65 (s, 1H), 7.03 (m, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.20 (s, 1H), 7.35 (d, J = 2.7 Hz, 1H), 8.05 (s, 1H), 8.14 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 8.19 (s, 1H)

Production Example 34: 6,7-Dimethoxy-4-quinazolone

Formamide (150 ml) was added to methyl 2-amino-3,4-dimethoxybenzoate (20.0 g, 94.8 mmol). The mixture was heated at 160°C for 8.5 hr. The reaction solution was cooled and was then filtered. The collected precipitate was washed with water (100 ml × 2 times), and the washed precipitate was dried in vacuo to give 17.85 g (yield 91.5%) of the target compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 4.01 (s, 3H), 4.02 (s, 3H), 7.14 (s, 1H), 7.34 (s, 1H), 7.61 (s, 1H), 7.97 (s, 1H)

Production Example 35: 4-Chloro-6,7-dimethoxyquinazoline

Sulfolane (250 ml) and phosphorus oxychloride (250 ml = 412.5 g, 2.69 mol) were added to 6,7-dimethoxy-4-quinazolone (50.1 g, 0.24 mol), and the mixture was stirred at 120°C for one hr. The reaction mixture was cooled to room temperature, and the excess phosphorus oxychloride was then removed by distillation under the reduced pressure. The residue was poured into ice water (1000 ml), and chloroform (1000 ml) was added thereto. The aqueous layer was adjusted to pH 6.5 by the addition of a 20% sodium hydroxide solution, followed by the separation of the organic layer from the aqueous layer.

The separated organic layer was washed with water (1000 ml × six times), was dried over sodium sulfate, and was then concentrated under the reduced pressure. Tetrahydrofuran (470 ml) was added to the residue, and the mixture was refluxed. The reaction solution was cooled to -5°C to -10°C and was filtered and dried to give 38.5 g (yield 71.4%) of the target product.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 4.09 (s, 3H), 4.09 (s, 3H), 7.14 (s, 1H), 7.34 (s, 1H), 7.61 (s, 1H), 7.97 (s, 1H)

Production Example 36: 4-Chloro-6,7-dimethoxyquinazoline

Toluene (100 ml) and phosphorus oxychloride (7.4 g, 48.6 mmol) were added to 6,7-dimethoxy-4-quinazolone (10.0 g, 48.5 mmol), and the mixture was stirred at 120°C for 6.5 hr. The reaction solution was cooled to room temperature, was then filtered, was washed with toluene (100 ml, 50 ml), and was dried to give 11.5 g (yield 91%) of the target product.

Production Example 37: 4-(4'-Amino-3'-chloro)-phenoxy-6,7-dimethoxyquinazoline

Sodium hydroxide (8.5 g, 0.21 mol) and water (90 ml) were added to and dissolved in 4-amino-3-chlorophenol hydrochloride (14.6 g, 81 mmol). 4-Chloro-6,7-dimethoxyquinazoline (12 g, 53 mmol) and methyl ethyl ketone (225 ml) were added to the solution, and the mixture was refluxed for 2 hr. The reaction solution was cooled to about 50°C, and chloroform (500 ml) and water (500 ml) were then added to the cooled reaction solution. The mixture was stirred for 10 min, and the organic layer was then separated from the aqueous layer. Chloroform (250 ml) was added to the aqueous layer, and the mixture was stirred for 10 min, followed by layer separation. The organic layer was concentrated under the reduced pressure. Methanol (50 ml) was added to the residue, and the mixture was stirred for 30 min. The reaction solution was then filtered and was dried to give 15.6 g (yield 85%) of the target product.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.95 (s, 3H), 3.97 (s, 3H), 5.33 (s, 2H), 6.85 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 7.36 (s, 1H), 7.51 (s, 1H), 8.53 (s, 1H)

Production Example 38: 4-(4'-Amino-3'-chloro)-phenoxy-6,7-dimethoxyquinazoline

A 20% aqueous sodium hydroxide solution (3.5 ml) and water (2 ml) were added to and dissolved in 4-amino-3-chlorophenol hydrochloride (1.3 g, 7.2 mmol). 4-Chloro-6,7-dimethoxyquinazoline (0.8 g, 3.6 mmol), chloroform (6 ml), and tetrabutylammonium bromide (0.58 g, 1.8 mmol) were added to the solution, and the mixture was refluxed for 2 hr. The reaction solution was cooled. Chloroform (10 ml) and water (10 ml) were then added to the cooled reaction solution, and the mixture was stirred for 10 min, followed by the separation of the organic layer from the aqueous layer. Chloroform (10 ml) was added to the separated aqueous layer, and the mixture was stirred for 10 min, followed by layer separation. The organic layer was concentrated under the reduced pressure. Methanol (2 ml) was added to the residue, and the mixture was stirred for 30 min. The reaction solution was then filtered and was dried to give 1.0 g (yield 83%) of the target product.

Example 1: N-(2,4-Difluorobenzyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (5.0 ml) and triethylamine (1.0 ml) with heating. A solution of triphosgene (103 mg) in dichloromethane (1.0 ml) was then added to the solution, and the mixture was heated under reflux for 3 min. Next, 2,4-difluorobenzylamine (54 mg) was added thereto, and the mixture was heated under reflux for additional 5 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over

anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 123 mg (yield 80%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.02 (s, 3H), 4.03 (s, 3H), 4.47 (d, J = 5.9 Hz, 2H), 5.78 - 5.90 (m, 1H), 6.46 (d, J = 5.4 Hz, 1H), 6.74 - 6.99 (m, 4H), 7.03 - 7.14 (m, 1H), 7.35 - 7.44 (m, 2H), 7.50 (s, 1H), 8.16 (t, J = 9.0 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 483 (M^+)

Example 2: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-fluoroethyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (10 ml) and triethylamine (0.5 ml) with heating. A solution of triphosgene (47 mg) in dichloromethane (1.0 ml) was then added to the solution, and the mixture was heated under reflux for 5 min. Next, 2-fluoroethylamine hydrochloride (42 mg) was added thereto, and the mixture was heated under reflux for additional 8 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 93 mg (yield 72%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.40 (m, 1H), 3.47 (m, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 4.42 (t, J = 4.9 Hz, 1H), 4.54 (t, J = 4.9 Hz, 1H), 6.51 (d, J = 5.4 Hz, 1H), 6.88 (m, 1H), 7.05 (m, 1H), 7.28 (dd, J = 2.7 Hz, J = 11.7 Hz, 1H), 7.40 (s, 1H), 7.49 (s, 1H), 8.21 (m, 1H), 8.47 (br, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 404 (M^++1)

Example 3: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-

fluorophenyl}-N'-(2-pyridylmethyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (5 ml) and triethylamine (1 ml). A solution of triphosgene (104 mg) in dichloromethane was then added to the solution, and the mixture was refluxed for 5 min. Next, 2-(aminomethyl)pyridine (40 µl) was added thereto, and the mixture was heated under reflux for 2 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) and chloroform (2 ml) were added to the reaction solution. The mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (8/1) to give 126 mg (yield 88%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.07 (s, 3H), 4.09 (s, 3H), 4.61 (d, J = 5.4 Hz, 2H), 6.40 - 6.50 (br, 1H), 6.61 (d, J = 5.9 Hz, 1H), 6.92 - 7.01 (m, 2H), 7.21 - 7.25 (m, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 7.68 - 7.78 (m, 2H), 7.75 (s, 1H), 8.27 - 8.34 (m, 1H), 8.49 (d, J = 6.1 Hz, 1H), 8.55 (d, J = 4.1 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 448 (M^+)

Example 4: N-Allyl-N'-{4-[(6,7-dimethoxy-4-quinolyl)-oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (5 ml) and triethylamine (1 ml), and a solution of triphosgene (104 mg) in dichloromethane was then added to the solution. The mixture was heated under reflux for 5 min. Next, allylamine (22 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 4 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) and chloroform (2 ml) were added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation

under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 125 mg (yield 98%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.91 - 3.96 (m, 2H), 4.06 (s, 3H), 4.09 (s, 3H), 5.14 - 5.20 (m, 1H), 5.26 - 5.33 (m, 1H), 5.58 - 5.66 (br, 1H), 5.86 - 5.98 (m, 1H), 6.56 (d, J = 5.9 Hz, 1H), 6.88 - 7.01 (m, 2H), 7.23 (s, 1H), 7.55 (s, 1H), 7.66 (s, 1H), 8.26 - 8.33 (m, 1H), 8.47 (d, J = 5.9 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 397 (M^+)

Example 5: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (10 ml) and triethylamine (2 ml), and a solution of triphosgene (104 mg) in dichloromethane was then added to the solution. The mixture was heated under reflux for 5 min. Next, propylamine (29 mg) was added, and the mixture was heated under reflux for 40 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 89 mg (yield 71%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.55 - 1.64 (m, 2H), 3.24 - 3.29 (m, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 5.11 (t, J = 5.4 Hz, 1H), 6.51 (d, J = 5.4 Hz, 1H), 6.74 - 6.76 (m, 1H), 6.91 - 6.99 (m, 2H), 7.48 (s, 1H), 7.52 (s, 1H), 8.18 - 8.23 (m, 1H), 8.49 (d, J = 5.6 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 399 (M^+)

Example 6: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(4-fluorobutyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (6 ml) and triethylamine (1.0 ml) with heating, and a solution of triphosgene (104 mg) in dichloromethane (1.0 ml) was then added to the solution. The mixture was heated under reflux for 5 min. Next, 4-fluorobutylamine hydrochloride (55 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 80 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.66 - 1.87 (m, 4H), 3.33 - 3.40 (m, 2H), 4.04 (s, 3H), 4.05 (s, 3H), 4.44 (t, J = 5.6 Hz, 1H), 4.56 (t, J = 5.7 Hz, 1H), 4.90 (t, J = 5.7 Hz, 1H), 6.48 - 6.52 (m, 2H), 6.93 - 7.02 (m, 2H), 7.42 (s, 1H), 7.51 (s, 1H), 8.15 (t, J = 8.9 Hz, 1H), 8.50 (d, J = 5.1 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 431 (M^+)

Example 7: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-propynyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (150 mg) was dissolved in chloroform (10 ml) and triethylamine (2 ml), and a solution of triphosgene (156 mg) in dichloromethane was added to the solution. The mixture was heated under reflux for 10 min. Next, propargylamine (53 mg) was added, and the mixture was heated under reflux for additional 30 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was

purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 164 mg (yield 87%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.49 - 2.51 (m, 1H), 3.90 - 3.95 (m, 8H), 6.52 (d, J = 5.1 Hz, 1H), 6.89 - 6.92 (m, 1H), 7.04 - 7.06 (m, 1H), 7.26 - 7.29 (m, 1H), 7.39 (s, 1H), 7.49 (s, 1H), 8.16 - 8.20 (m, 1H), 8.46 - 8.49 (m, 2H)

Example 8: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-ethylurea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (8 ml) and triethylamine (1.0 ml) with heating, and a solution of triphosgene (47 mg) in toluene (1.0 ml) was then added to the solution. The mixture was heated under reflux for 5 min. Next, ethylamine hydrochloride (60 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 5 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 70 mg (yield 53%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.21 (t, J = 7.3 Hz, 3H), 3.34 (m, 2H), 4.06 (s, 3H), 4.08 (s, 3H), 5.64 (br, 1H), 6.55 (d, J = 5.6 Hz, 1H), 6.89 (dd, J = 2.7 Hz, J = 11.2 Hz, 1H), 6.97 (m, 1H), 7.26 (br, 1H), 7.54 (s, 1H), 7.62 (s, 1H), 8.28 (t, J = 9.0 Hz, 1H), 8.47 (d, J = 5.6 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 386 (M^++1)

Example 9: N-Butyl-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (8 ml) and

triethylamine (1.0 ml) with heating, and a solution of triphosgene (47 mg) in toluene (1.0 ml) was then added to the solution. The mixture was heated under reflux for 5 min. Next, butylamine (80 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 5 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 117 mg (yield 81%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.55 (m, 2H), 3.29 (dd, J = 7.1 Hz, J = 12.9 Hz, 2H), 4.06 (s, 3H), 4.09 (s, 3H), 5.72 (br, 1H), 6.56 (d, J = 5.9 Hz, 1H), 6.88 (dd, J = 2.7 Hz, J = 11.2 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 7.33 (s, 1H), 7.55 (s, 1H), 7.65 (s, 1H), 8.30 (t, J = 9.0 Hz, 1H), 8.46 (d, J = 5.9 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 414 (M^++1)

Example 10: N-(sec-Butyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (104 mg) in dichloromethane was then added to the solution. The mixture was heated under reflux for 5 min. Next, sec-butylamine (48 µl) was added to the reaction solution. The mixture was heated under reflux for 10 min. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (8/2) to give 117 mg (yield 89%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, J = 7.6 Hz, 3H),

1.18 (d, J = 6.6 Hz, 3H), 1.47 - 1.55 (m, 2H), 3.79 - 3.89 (m, 1H), 4.04 (s, 6H), 5.28 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 5.4 Hz, 1H), 6.89 - 6.98 (m, 2H), 7.08 (d, J = 2.7 Hz, 1H), 7.42 (s, 1H), 7.51 (s, 1H), 8.20 - 8.24 (m, J = 9.0 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 414 (M^++1)

Example 11: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-isobutylurea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (104 mg) in dichloromethane was then added to the solution. The mixture was heated under reflux for 5 min. Next, isobutylamine (50 µl) was added to the reaction solution, and the mixture was heated under reflux for 10 min. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (4/1). Thus, the title compound was quantitatively obtained.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.94 (d, J = 6.6 Hz, 6H), 1.77 - 1.84 (m, 1H), 3.10 - 3.13 (m, 2H), 4.03 (s, 3H), 4.03 (s, 3H), 5.58 (t, J = 5.4 Hz, 1H), 6.47 (d, J = 5.4 Hz, H), 6.88 - 6.97 (m, 2H), 7.18 (s, 1H), 7.41 (s, 1H), 7.50 (s, 1H), 8.18 - 8.23 (m, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 414 (M^++1)

Example 12: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(1,2-dimethylpropyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (47 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 1,2-dimethylpropylamine (55 µl) was added to the reaction solution, and the mixture was stirred at room temperature for 10 min. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development

with chloroform/acetone (2/1) to give 89 mg (yield 65%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.93 (d, J = 2.2 Hz, 3H), 0.95 (d, J = 2.4 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.72 - 1.80 (m, 1H), 3.76 - 3.84 (m, 1H), 4.04 (s, 3H), 4.05 (s, 3H), 4.91 (d, J = 8.5 Hz, 1H), 6.48 (d, J = 5.4 Hz, 1H), 6.74 (d, J = 2.9 Hz, 1H), 6.91 - 6.98 (m, 2H), 7.42 (s, 1H), 7.51 (s, 1H), 8.18 - 8.23 (m, 1H), 8.49 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 428 (M^++1)

Example 13: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-propylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (100 mg) was dissolved in chloroform (7.5 ml) and triethylamine (1 ml), and a solution of triphosgene (99 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min. Next, n-propylamine (21 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (8/1). Thus, the title compound was quantitatively obtained.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, J = 7.3 Hz, 3H), 1.58 - 1.65 (m, 2H), 3.24 - 3.31 (m, 2H), 4.04 (s, 3H), 4.05 (s, 3H), 4.94 (t, J = 5.9 Hz, 1H), 6.48 (d, J = 5.1 Hz, 1H), 6.77 (s, 1H), 7.11 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.43 (s, 1H), 7.52 (s, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.50 (d, J = 5.1 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 415, 417 (M^+)

Example 14: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-fluoro-2-methylphenyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline

(122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-fluoro-2-methylaniline (126 µl) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 142 mg (yield 79%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 4.04 (s, 3H), 4.04 (s, 3H), 6.31 (s, 1H), 6.47 (d, J = 5.1 Hz, 1H), 6.97 - 7.06 (m, 3H), 7.11 - 7.14 (m, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.41 - 7.44 (m, 2H), 7.50 (s, 1H), 8.35 (d, J = 9.0 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 482, 484 (M^++1)

Example 15: N-(5-Bromo-6-methyl-2-pyridyl)-N'-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-3-bromo-2-methylpyridine (208 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 155 mg (yield 77%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.69 (s, 3H), 4.06 (s, 6H), 6.53 (d, J = 5.4 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 7.14 - 7.17 (m, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.44 (s, 1H), 7.53 (s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.93 (s,

1H), 8.49 (d, J = 9.0 Hz, 1H), 8.52 (d, J = 5.4 Hz, 1H), 11.92 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 543, 545, 547 (M^++1)

Example 16: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-chloro-2-pyridyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-chloropyridine (143 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 148 mg (yield 82%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.06 (s, 3H), 4.06 (s, 3H), 6.53 (d, J = 5.1 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 7.14 - 7.17 (m, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.44 (s, 1H), 7.53 (s, 1H), 7.64 - 7.67 (m, 1H), 8.28 (d, J = 2.7 Hz, 1H), 8.50 - 8.53 (m, 2H), 8.92 (s, 1H), 12.11 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 485, 487, 489 (M^++1)

Example 17: N-(5-Bromo-2-pyridyl)-N'-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-bromopyridine (192 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction

solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 108 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.06 (s, 3H), 4.06 (s, 3H), 6.53 (d, J = 5.1 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 7.14 - 7.18 (m, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.45 (s, 1H), 7.53 (s, 1H), 7.77 - 7.80 (m, 1H), 8.15 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 9.0 Hz, 1H), 8.52 (d, J = 5.4 Hz, 1H), 12.09 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 529, 531, 533 (M^++1)

Example 18: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methoxyphenyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (100 mg) was dissolved in chloroform(10 ml), and 2-methoxyphenyl isocyanate (54 mg) was added to the solution. The mixture was stirred at 60°C overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (6/4) to give 111 mg (yield 77%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.50 (d, J = 5.1 Hz, 1H), 6.89 - 6.93 (m, 1H), 6.98 - 7.03 (m, 1H), 7.05 - 7.10 (m, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.35 (s, 1H), 7.36 (s, 1H), 7.44 (s, 1H), 7.52 (s, 1H), 8.05 - 8.07 (m, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.52 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 480, 482 (M^++1)

Example 19: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methylphenyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml), and o-toluyl isocyanate (59 mg) was added to the solution. The

mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal. The crystal was collected by filtration to give 59 mg (yield 34%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.22 (s, 1H), 6.47 (d, J = 5.1 Hz, 1H), 7.01 (s, 1H), 7.11 - 7.14 (m, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.25 - 7.35 (m, 3H), 7.42 (s, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.50 (s, 1H), 8.37 (d, J = 8.8 Hz, 1H), 8.50 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 464, 466 (M^++1)

Example 20: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-2-pyridyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-picoline (120 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 119 mg (yield 69%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.31 (s, 3H), 4.06 (s, 6H), 6.53 (d, J = 5.4 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 7.13 - 7.16 (m, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.43 (s, 1H), 7.49 - 7.52 (m, 1H), 7.54 (s, 1H), 8.00 (s, 1H), 8.14 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.55 (d, J = 9.0 Hz, 1H), 12.57 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 465, 467 (M^++1)

Example 21: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(6-methyl-2-pyridyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-2-picoline (120 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 73 mg (yield 42%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.57 (s, 3H), 4.06 (s, 6H), 6.54 (d, J = 5.4 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 7.15 - 7.18 (m, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.44 (s, 1H), 7.54 - 7.59 (m, 2H), 8.36 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.57 (d, J = 9.0 Hz, 1H), 12.45 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 465, 467 (M^++1)

Example 22: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-methoxyphenyl)urea hydrochloride

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (100 mg) was dissolved in chloroform (4 ml), and 4-methoxyphenyl isocyanate (60 μl) was then added to the solution. A reaction was then allowed to proceed at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added thereto. The resultant precipitate was collected by suction filtration to give 90 mg (yield 67%) of N-2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl-N'-(4-methoxy-phenyl)urea. This product was suspended in 4 ml of methanol, and a

hydrochloric acid-methanol solution was added to the suspension. The mixture was stirred at room temperature for 4 hr, and the solvent was then removed by distillation to give the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 6.90 (d, J = 9.3 Hz, 2H), 6.97 (d, J = 6.6 Hz, 1H), 7.37 - 7.41 (m, 3H), 7.62 (s, 1H), 7.67 (d, J = 2.7 Hz, 1H), 8.39 (d, J = 9.0 Hz, 1H), 8.49 (s, 1H), 8.82 (d, J = 6.6 Hz, 1H), 9.49 (s, 1H)

Example 23: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(1-naphthyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml), and 1-naphthyl isocyanate (75 mg) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal. The crystal was collected by filtration to give 105 mg (yield 57%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.03 (s, 3H), 4.04 (s, 3H), 6.44 (d, J = 5.4 Hz, 1H), 6.72 (s, 1H), 7.10 - 7.13 (m, 3H), 7.41 (s, 1H), 7.48 (s, 1H), 7.55 - 7.69 (m, 4H), 7.88 - 7.96 (m, 2H), 8.15 (d, J = 7.6 Hz, 1H), 8.38 - 8.40 (m, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 500, 502 (M^++1)

Example 24: N-(2,4-Difluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (710 mg) was dissolved in chloroform (7 ml), and 2,4-difluorophenyl isocyanate (310 μl) was then added to the solution. The mixture was heated under reflux for one hr, and a large amount of ether was added to the reaction solution. The resultant precipitate was collected by suction filtration to give 735 mg (yield

70%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 2.27 (s, 3H), 4.04 (s, 3H), 4.06 (s, 3H), 6.27 (d, J = 5.4 Hz, 1H), 6.78 - 6.89 (m, 2H), 6.95 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.10 (s, 1H), 7.40 - 7.45 (m, 2H), 7.61 (s, 1H), 8.03 - 8.12 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FAB-MS, m/z): 480 (M^++1)

Example 25: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}-N'-(4-fluoro-2-methylphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-fluoro-2-methylaniline (126 μl) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 160 mg (yield 91%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 3H), 2.22 (s, 3H), 2.25 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.24 (d, J = 5.1 Hz, 1H), 6.33 (s, 1H), 6.42 (s, 1H), 6.94 - 7.03 (m, 3H), 7.43 (s, 1H), 7.46 - 7.55 (m, 2H), 7.60 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 476 (M^++1)

Example 26: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}-N'-(3-fluoro-2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 3-fluoro-o-anisidine (132 μl) was added to the reaction solution, and the mixture

was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 23 mg (yield 13%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.15 (s, 3H), 2.32 (s, 3H), 3.84 (d, J = 1.7 Hz, 3H), 4.05 (s, 3H), 4.08 (s, 3H), 6.28 (d, J = 5.4 Hz, 1H), 6.72 - 6.77 (m, 1H), 6.96 - 7.09 (m, 3H), 7.43 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.60 (s, 1H), 7.62 (s, 1H), 8.02 - 8.05 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 492 (M^++1)

Example 27: N-(5-Bromo-6-methyl-2-pyridyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-3-bromo-2-methylpyridine (208 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 103 mg (yield 52%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.42 (s, 3H), 2.65 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.32 (d, J = 5.1 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.64 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 8.29 (s, 1H), 8.45 (d, J = 5.4 Hz, 1H), 11.30 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 537, 539 (M^++1)

Example 28: N-(5-Chloro-2-pyridyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (3.00 g) was dissolved in chloroform (150 ml) and triethylamine (6 ml), and a solution of triphosgene (2.74 g) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-chloropyridine (2.38 g) was added to the reaction solution, and the mixture was then stirred at room temperature for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/methanol (20/1) to give 3.4 g (yield 77%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.38 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.31 (d, J = 5.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.62 - 7.68 (m, 2H), 7.90 (d, J = 8.8 Hz, 1H), 8.23 (d, J = 2.4 Hz, 1H), 8.45 (d, J = 5.4 Hz, 1H), 8.50 (s, 1H), 11.23 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 479, 481 (M^++1)

Example 29: N-(5-Bromo-2-pyridyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-bromopyridine (192 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9). The solvent was removed by

distillation, and a crystal was precipitated from a minor amount of methanol and a large amount of ether. The crystal was collected by filtration to give 80 mg (yield 41%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.38 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 7.45 (s, 1H), 7.64 (s, 1H), 7.75 - 7.77 (m, 1H), 7.89 (d, J = 8.8 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.45 (d, J = 5.4 Hz, 1H), 8.81 (s, 1H), 11.17 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 523, 525 (M^++1)

Example 30: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}-N'-(2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml), and 2-methoxyphenyl isocyanate (60 μl) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added thereto to precipitate a crystal which was then collected by filtration to give 131 mg (yield 75%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.32 (s, 3H), 3.81 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.25 (s, 1H), 6.26 (d, J = 5.4 Hz, 1H), 6.85 - 6.87 (m, 1H), 6.97 - 7.07 (m, 4H), 7.41 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.62 (s, 1H), 8.15 - 8.17 (m, 1H), 8.45 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 474 (M^++1)

Example 31: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}-N'-(2-methylphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml), and o-toluyl isocyanate (55 μl) was added to the solution. The mixture was stirred at room temperature

overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 130 mg (yield 70%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 3H), 2.22 (s, 3H), 2.26 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 6.23 - 6.28 (m, 3H), 7.02 (d, J = 8.5 Hz, 1H), 7.14 - 7.17 (m, 1H), 7.24 - 7.29 (m, 2H), 7.43 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.63 (d, J = 7.3 Hz, 1H), 8.43 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 458 (M^++1)

Example 32: N-(4-Chloro-2-methylphenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-chloro-2-methylaniline (130 µl) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 136 mg (yield 75%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 2.18 (s, 3H), 2.27 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 6.24 (d, J = 5.4 Hz, 1H), 6.33 (s, 1H), 6.40 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.19 - 7.21 (m, 2H), 7.42 - 7.44 (m, 2H), 7.60 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 492, 494 (M^++1)

Example 33: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-

dimethylphenyl}-N'-(2-pyridyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-aminopyridine (104 mg) was added to the reaction solution, and the mixture was heated under reflux overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 72 mg (yield 44%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.41 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.32 (d, J = 5.4 Hz, 1H), 6.92 - 6.98 (m, 2H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.65 (s, 1H), 7.67 - 7.69 (m, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.25 - 8.27 (m, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.72 (s, 1H), 11.77 (br, 1H)

Mass analysis, found (ESI-MS, m/z): 445 (M^++1)

Example 34: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}-N'-(5-methyl-2-pyridyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-picoline (120 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 122 mg (yield 72%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.15 (s, 3H), 2.28 (s,

3H), 2.39 (s, 3H), 4.04 (s, 3H), 4.07 (s, 3H), 6.32 (d, J = 5.4 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.43 (s, 1H), 7.45 - 7.48 (m, 1H), 7.64 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 1.5 Hz, 1H), 8.44 (d, J = 5.4 Hz, 1H), 9.23 (s, 1H), 11.77 (br, 1H)

Mass analysis, found (FD-MS, m/z): 458 (M^+)

Example 35: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}-N'-(6-methyl-2-pyridyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-2-picoline (120 mg) was added to the reaction solution, and the mixture was heated under reflux overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (40/60) to give 64 mg (yield 38%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.44 (s, 3H), 2.54 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.32 (d, J = 5.4 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.53 - 7.57 (m, 1H), 7.65 (s, 1H), 7.79 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H), 11.76 (br, 1H)

Mass analysis, found (FD-MS, m/z): 458 (M^+)

Example 36: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}-N'-(4-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,3-dimethylaniline (100 mg) was dissolved in chloroform (4 ml), and 4-methoxyphenyl isocyanate (60 μl) was then added to the solution. The mixture was allowed to react at room temperature overnight, and the solvent was removed by distillation under the reduced pressure. The residue was

dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution. The resultant precipitate was then collected by suction filtration to give 115 mg (yield 78%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 3H), 2.30 (s, 3H), 3.76 (s, 3H), 4.06 (s, 3H), 4.12 (s, 3H), 6.46 (d, J = 6.3 Hz, 1H), 6.78 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 9.0 Hz, 2H), 7.67 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H), 8.20 - 8.23 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 474 (M^++1)

Example 37: N-(2,4-Difluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (200 mg) was dissolved in chloroform (15 ml), and 2,4-difluorophenyl isocyanate (88 µl) was then added to the solution. The mixture was heated under reflux for one hr. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (4/1) to give 287 mg (yield 97%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.26 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.31 (d, J = 5.4 Hz, 1H), 6.57 (s, 1H), 6.81 - 6.95 (m, 3H), 7.00 (s, 1H), 7.43 (s, 1H), 7.55 (s, 1H), 7.59 (s, 1H), 8.05 - 8.13 (m, 1H), 8.47 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 479 (M^+)

Example 38: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (150 mg) was dissolved in chloroform (13 ml) and triethylamine (1.5 ml), and a solution of triphosgene (151 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min. Next, n-propylamine (33 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate

solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (4/1) to give 178 mg (yield 95%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, J = 7.3 Hz, 3H), 1.51 - 1.65 (m, 2H), 2.15 (s, 3H), 2.26 (s, 3H), 3.21 - 3.28 (m, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 4.63 - 4.69 (m, 1H), 5.97 (s, 1H), 6.31 (d, J = 5.1 Hz, 1H), 6.98 (s, 1H), 7.43 (s, 2H), 7.58 (s, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 409 (M^+)

Example 39: N-(4-Chloro-2-methylphenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-chloro-2-methylaniline (44 µl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 118 mg (yield 78%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.21 (s, 3H), 2.23 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.28 (d, J = 5.4 Hz, 1H), 6.30 (s, 1H), 6.32 (s, 1H), 6.98 (s, 1H), 7.22 - 7.23 (m, 2H), 7.43 (s, 1H), 7.58 (s, 1H),

7.59 - 7.63 (m, 2H), 8.45 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 492, 494 (M^++1)

Example 40: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}-N'-(4-fluoro-2-methylphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-fluoro-2-methylaniline (42 µl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 108 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.15 (s, 6H), 2.30 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.24 (s, 2H), 6.28 (d, J = 5.1 Hz, 1H), 6.94 (s, 1H), 6.96 - 7.00 (m, 2H), 7.42 (s, 1H), 7.49 - 7.52 (m, 1H), 7.58 (s, 1H), 7.64 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 476 (M^++1)

Example 41: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}-N'-(3-fluoro-2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 3-fluoro-o-anisidine (44 µl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium

hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 126 mg (yield 83%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.27 (s, 3H), 3.83 (d, J = 1.7 Hz, 3H), 4.04 (s, 3H), 4.07 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.74 - 6.79 (m, 1H), 6.97 - 7.03 (m, 3H), 7.44 (s, 1H), 7.57 (s, 1H), 7.60 (s, 1H), 7.66 (s, 1H), 8.02 - 8.04 (m, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 492 (M^++1)

Example 42: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}-N'-(2-methylphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml), and o-toluyl isocyanate (46 μl) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 111 mg (yield 79%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 6H), 2.26 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 6.27 (d, J = 5.1 Hz, 1H), 6.77 (s, 1H), 6.81 (s, 1H), 6.91 (s, 1H), 7.11 - 7.15 (m, 1H), 7.22 (s, 1H), 7.24 (s, 1H), 7.42 (s, 1H), 7.59 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.68 (s, 1H), 8.43 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 458 (M^++1)

Example 43: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}-N'-(2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml),

and 2-methoxyphenyl isocyanate (49 µl) was added to the solution. The mixture was heated under reflux overnight. Methanol was added to the reaction solution. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to quantitatively give the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 2.24 (s, 3H), 3.75 (s, 3H), 4.03 (s, 3H), 4.07 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.84 - 6.87 (m, 1H), 6.95 - 7.03 (m, 3H), 7.06 (s, 1H), 7.44 (s, 1H), 7.56 (s, 1H), 7.61 (s, 1H), 7.63 (s, 1H), 8.17 - 8.20 (m, 1H), 8.46 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 474 (M^++1)

Example 44: N-(5-Bromo-6-methyl-2-pyridyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-3-bromo-2-methylpyridine (69 mg) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a larger amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 80 mg (yield 48%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.18 (s, 3H), 2.42 (s, 3H), 2.65 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.34 (d, J = 5.4 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 6.98 (s, 1H), 7.43 (s, 1H), 7.62 (s, 1H), 7.70 (s, 1H), 7.74 (d, J =

8.5 Hz, 1H), 8.05 (s, 1H), 8.46 (d, J = 5.4 Hz, 1H), 11.17 (br, 1H)

Mass analysis, found (ESI-MS, m/z): 537, 539 (M^++1)

Example 45: N-(2,6-Dimethoxy-3-pyridyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 3-amino-2,6-dimethoxypyridine (70 mg) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 124 mg (yield 79%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.27 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.34 (d, J = 8.5 Hz, 1H), 6.36 (s, 1H), 6.74 (s, 1H), 6.99 (s, 1H), 7.44 (s, 1H), 7.57 (s, 1H), 7.60 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 8.46 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 505 (M^++1)

Example 46: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}-N'-(4-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2,5-dimethylaniline (100 mg) was dissolved in chloroform (4 ml), and 4-methoxyphenyl isocyanate (60 μl) was then added to the solution. The mixture was allowed to react at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was

dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution. The resultant precipitate was collected by suction filtration to give 110 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 3H), 2.26 (s, 3H), 3.76 (s, 3H), 4.03 (s, 3H), 4.08 (s, 3H), 6.39 (d, J = 6.1 Hz, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.87 (s, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.55 (br, 1H), 7.62 (s, 1H), 7.67 (s, 1H), 7.80 (s, 1H), 8.19 (br, 1H), 8.27 (d, J = 6.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 474 (M^++1)

Example 47: N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-nitrophenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-nitroaniline (150 mg) was dissolved in chloroform (10 ml) and triethylamine (1.5 ml), and a solution of triphosgene (144 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min. Next, n-propylamine (31 mg) was added. The mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (4/1) to give 160 mg (yield 86%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.5 Hz, 3H), 1.59 - 1.69 (m, 2H), 3.27 - 3.34 (m, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 4.95 - 5.01 (br, 1H), 6.47 (d, J = 5.4 Hz, 1H), 7.43 - 7.51 (m, 3H), 8.04 (d, J = 2.7 Hz, 1H), 8.53 (d, J = 5.4 Hz, 1H), 8.81 (d, J = 9.3 Hz, 1H), 9.74 - 9.79 (br, 1H)

Mass analysis, found (FD-MS, m/z): 426 (M^+)

Example 48: N-(2,4-Difluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2-nitrophenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2-nitroaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (96 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min. Next, 2,4-difluoroaniline (45 mg) was added to the reaction solution, and the mixture was further heated under reflux overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/acetone (3/1) to give 81 mg (yield 56%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.06 (s, 3H), 6.50 (d, J = 5.1 Hz, 1H), 6.91 - 6.98 (m, 3H), 7.45 (s, 1H), 7.49 (s, 1H), 7.50 - 7.54 (m, 1H), 7.88 - 7.97 (m, 1H), 8.05 (d, J = 2.9 Hz, 1H), 8.54 (d, J = 5.1 Hz, 1H), 8.77 (d, J = 9.3 Hz, 1H), 9.98 (s, 1H)

Mass analysis, found (FD-MS, m/z): 496 (M^+)

Example 49: N-{3,5-Dichloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2,4-difluorophenyl)urea

3,5-Dichloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]-aniline (53 mg) was dissolved in chloroform (5 ml), and 2,4-difluorophenyl isocyanate (34 μl) was added to the solution. The mixture was heated under reflux overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 56 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.09 (s, 3H), 6.26 (d, J = 5.4 Hz, 1H), 6.86 - 6.93 (m, 2H), 7.05 (s, 1H), 7.44 (s, 1H), 7.46 (s, 1H), 7.60 (s, 2H), 7.64 (s, 1H), 8.01 - 8.05 (m, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FAB-MS, m/z): 520, 522, 524 (M^++1)

Example 50: N-(2,4-Difluorophenyl)-N'-(2-fluoro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)-urea

N-(2,4-Difluorophenyl)-N'-{2-fluoro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}urea (20 mg), potassium carbonate (7 mg), tetra-n-butylammonium iodide (2 mg), and N-(2-chloroethyl)morpholine hydrochloride (10 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 70°C overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (30/1) to give 14 mg (yield 57%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.57 (t, J = 4.4 Hz, 4H), 2.88 (m, 2H), 3.69 (t, J = 4.4 Hz, 4H), 3.94 (s, 3H), 4.26 (t, J = 5.9 Hz, 2H), 6.43 (d, J = 5.1 Hz, 1H), 6.77 - 6.95 (m, 4H), 7.35 (s, 1H), 7.43 (s, 1H), 7.96 - 8.02 (m, 1H), 8.13 - 8.17 (m, 1H), 8.44 (d, J = 5.1 Hz, 1H)

Example 51: N-(2-Chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)urea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)-oxy]phenyl}-N'-(2,4-difluorophenyl)urea (174 mg) was dissolved in N,N-dimethylformamide (9 ml), and potassium carbonate (64 mg), tetra-n-butylammonium iodide (14 mg), and N-(2-chloroethyl)morpholine hydrochloride (86 mg) were then added to the solution. The mixture was stirred at 70°C for 17 hr, and a saturated aqueous sodium hydrogencarbonate solution was then added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over

anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (20/1) to give 75 mg (yield 35%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.60 - 2.67 (m, 4H), 2.95 (t, J = 6.0 Hz, 2H), 3.71 - 3.79 (m, 4H), 4.01 (s, 3H), 4.33 (t, J = 6.0 Hz, 2H), 6.50 (d, J = 5.1 Hz, 1H), 6.85 - 6.97 (m, 2H), 7.09 - 7.17 (m, 2H), 7.22 - 7.27 (m, 2H), 7.42 (s, 1H), 7.50 (s, 1H), 7.97 - 8.01 (m, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 585, 587 (M^++1)

Example 52: N-(2,4-Difluorophenyl)-N'-(4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-2,5-dimethylphenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2,4-difluorophenyl)urea (366 mg) was dissolved in N,N-dimethylformamide (6 ml), and palladium hydroxide (366 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in chloroform and methanol. The reaction solution was filtered through Celite. Next, the solvent was removed by distillation under the reduced pressure. The residue (213 mg), potassium carbonate (109 mg), tetra-n-butylammonium iodide (12 mg), and N-(2-chloroethyl)morpholine hydrochloride (74 mg) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at 70°C overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 106

mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.27 (s, 3H), 2.64 (t, J = 4.6 Hz, 4H), 2.96 (t, J = 6.0 Hz, 2H), 3.76 (t, J = 4.6 Hz, 4H), 4.03 (s, 3H), 4.34 (t, J = 6.0 Hz, 2H), 6.31 (d, J = 5.4 Hz, 1H), 6.47 (s, 1H), 6.81 - 6.92 (m, 3H), 7.00 (s, 1H), 7.43 (s, 1H), 7.54 (s, 1H), 7.58 (s, 1H), 8.05 - 8.12 (m, 1H), 8.47 (d, J = 5.4 Hz, 1H)

Example 53: N-(4-{[6-Methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2-methoxyphenyl)-urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2-methoxyphenyl)urea (363 mg) was dissolved in N,N-dimethylformamide (6 ml), and palladium hydroxide (363 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in chloroform and methanol, and the solution was filtered through Celite. Next, the solvent was removed by distillation under the reduced pressure. The residue (191 mg), potassium carbonate (219 mg), tetra-n-butylammonium iodide (12 mg), and N-(2-chloroethyl)morpholine hydrochloride (148 mg) were dissolved in N,N-dimethylformamide (5 ml). The solution was stirred at 70°C overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 101 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.28 (s, 3H), 2.64 (t, J = 4.5 Hz, 4H), 2.96 (t, J = 5.9 Hz, 2H), 3.76 (t, J = 4.6 Hz, 4H), 3.83 (s, 3H), 4.04 (s, 3H),

4.34 (t, J = 6.0 Hz, 2H), 6.30 (d, J = 5.4 Hz, 2H), 6.86 - 6.90 (m, 1H), 6.96 - 7.06 (m, 3H), 7.16 (s, 1H), 7.43 (s, 1H), 7.57 (s, 1H), 7.59 (s, 1H), 8.11 - 8.16 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Example 54: N-(2-Chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)urea

Sodium hydride (60 wt%, 153 mg) was added to dimethyl sulfoxide (2 ml), and the mixture was stirred at 60°C for 30 min and was then cooled to room temperature. 4-Amino-3-chlorophenol hydrochloride (343 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 10 min. Next, a solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)-quinoline (254 mg) in dimethyl sulfoxide (2 ml) was added to the reaction solution. The mixture was stirred at 110°C overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (7/3) to give 332 mg of a mixture containing 2-chloro-4-{[(6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}aniline as a major product. A 83 mg portion of the mixture was dissolved in chloroform (5 ml), and 2,4-difluorophenyl isocyanate (32 μl) was added to the solution. The mixture was heated under reflux overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 50 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.75 - 3.77 (m, 2H), 3.94 (s, 3H), 4.27 - 4.29 (m, 2H), 6.55 (d, J = 5.1 Hz, 1H), 7.04 - 7.09 (m, 1H), 7.25 - 7.36 (m, 2H), 7.42 (s,

1H), 7.50 (s, 1H), 7.51 (s, 1H), 8.09 - 8.15 (m, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.82 (s, 1H), 9.31 (s, 1H)

Example 55: N-(2-Chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}phenyl)-N'-(2-methoxyphenyl)urea

Sodium hydride (60 wt%, 153 mg) was added to dimethyl sulfoxide (2 ml), and the mixture was stirred at 60°C for 30 min and was then cooled to room temperature. 4-Amino-3-chlorophenol hydrochloride (343 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 10 min. Next, a solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline (254 mg) in dimethyl sulfoxide (2 ml) was added to the reaction solution, and the mixture was stirred at 110°C overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (7/3) to give 332 mg of a mixture containing 2-chloro-4-{[(6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}aniline as a main product. A 83 mg portion of the mixture was dissolved in chloroform (5 ml), and 2-methoxyphenyl isocyanate (35 µl) was added to the solution. The mixture was heated under reflux overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 31 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.75 - 3.77 (m, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 4.27 - 4.29 (m, 2H), 6.55 (d, J = 5.1 Hz, 1H), 6.89 - 7.05 (m, 3H), 7.24 - 7.27 (m, 1H), 7.42 (s, 1H), 7.48 (d, J = 2.7 Hz, 1H), 7.50 (s,

1H), 8.08 - 8.11 (m, 1H), 8.18 - 8.22 (m, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.99 - 9.03 (m, 2H)

Example 56: N-(2,4-Difluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2,3-dimethylphenyl)-urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,3-dimethylphenyl)-N'-(2,4-difluorophenyl)urea (213 mg) was dissolved in N,N-dimethylformamide (5 ml) and triethylamine (1 ml), and palladium hydroxide (40 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through Celite and was then washed with chloroform/methanol. The solvent was removed by distillation under the reduced pressure. A 90 mg portion of the residue (184 mg) was dissolved in N,N-dimethylformamide (1.5 ml), and potassium carbonate (32 mg), tetra-n-butylammonium iodide (7 mg), and 2-bromoethyl methyl ether (32 mg) were added to the solution. The mixture was stirred at 70°C overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/acetone (2/1) to give 110 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.97 (s, 3H), 2.17 (s, 3H), 3.31 (s, 3H), 3.70 (t, J = 4.4 Hz, 2H), 3.90 (s, 3H), 4.21 (t, J = 4.4 Hz, 2H), 6.18 (d, J = 5.1 Hz, 1H), 6.95 - 6.98 (m, 2H), 7.22 - 7.31 (m, 1H), 7.34 (s, 1H), 7.51 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 8.03 - 8.10 (m, 1H), 8.36 (d, J = 5.1 Hz, 1H), 8.38 (s, 1H), 8.79 (s, 1H)

Example 57: N-(4-{[6-Methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2,3-dimethylphenyl)-N'-(2-methoxyphenyl)-urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,3-dimethylphenyl)-N'-(2-methoxyphenyl)urea (161 mg) was dissolved in N,N-dimethylformamide (4 ml) and triethylamine (1 ml), and palladium hydroxide (32 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through Celite and was washed with chloroform/methanol. The solvent was removed by distillation under the reduced pressure. A 110 mg portion of the residue (223 mg) was dissolved in N,N-dimethylformamide (1.5 ml), and potassium carbonate (23 mg), tetra-n-butylammonium iodide (5 mg), and 2-bromoethyl methyl ether (23 mg) were added to the solution. The mixture was stirred at 70°C overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/acetone (2/1) to give 89 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.00 (s, 3H), 2.17 (s, 3H), 3.70 (t, J = 4.2 Hz, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 4.22 (t, J = 4.2 Hz, 2H), 6.19 (d, J = 5.1 Hz, 1H), 6.81 - 6.88 (m, 2H), 6.94 - 6.97 (m, 2H), 7.34 (s, 1H), 7.51 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.36 (d, J = 5.1 Hz, 1H), 8.48 (s, 1H), 8.58 (s, 1H)

Example 58: N-(2,4-Difluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2,4-difluorophenyl)urea (366 mg) was dissolved in N,N-dimethylformamide (6 ml), and palladium hydroxide (366 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by

distillation under the reduced pressure. The residue was dissolved in chloroform and methanol, and the solution was filtered through Celite. Next, the solvent was removed by distillation under the reduced pressure. The residue (213 mg), potassium carbonate (109 mg), tetra-n-butylammonium iodide (12 mg), and 2-bromoethyl methyl ether (40 μl) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at 70°C overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 124 mg (yield 73%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.26 (s, 3H), 3.49 (s, 3H), 3.90 (t, J = 4.8 Hz, 2H), 4.03 (s, 3H), 4.34 (t, J = 4.8 Hz, 2H), 6.30 (d, J = 5.1 Hz, 1H), 6.57 (s, 1H), 6.81 - 6.95 (m, 3H), 7.00 (s, 1H), 7.43 (s, 1H), 7.55 (s, 1H), 7.57 (s, 1H), 8.05 - 8.14 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 524 (M^++1)

Example 59: N-(4-{[6-Methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2-methoxyphenyl)-urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2-methoxyphenyl)urea (363 mg) was dissolved in N,N-dimethylformamide (6 ml), and palladium hydroxide (363 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure, and the residue was dissolved in chloroform and methanol. The solution was filtered through Celite. Next, the solvent was removed by distillation under the reduced pressure. The

residue (191 mg), potassium carbonate (110 mg), tetra-n-butylammonium iodide (12 mg), and 2-bromoethyl methyl ether (80 mg) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at 70°C overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 128 mg (yield 76%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.28 (s, 3H), 3.49 (s, 3H), 3.83 (s, 3H), 3.90 (t, J = 4.8 Hz, 2H), 4.04 (s, 3H), 4.35 (t, J = 4.9 Hz, 2H), 6.30 (d, J = 5.4 Hz, 1H), 6.33 (s, 1H), 6.86 - 6.90 (m, 1H), 6.96 - 7.06 (m, 3H), 7.17 (s, 1H), 7.43 (s, 1H), 7.56 (s, 1H), 7.58 (s, 1H), 8.12 - 8.17 (m, 1H), 8.45 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 518 (M^++1)

Example 60: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,3-dimethylphenyl)-N'-(2-methoxyphenyl)-urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,3-dimethylaniline (260 mg) was dissolved in N,N-dimethylformamide (5 ml), and 2-methoxyphenyl isocyanate (116 mg) was then added to the solution. The mixture was allowed to react at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/acetone (2/1) to give 169 mg (yield 47%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.99 (s, 3H), 2.02 (s,

3H), 3.83 (s, 3H), 3.90 (s, 3H), 5.25 (s, 2H), 6.18 (d, J = 5.3 Hz, 1H), 6.81 - 6.87 (m, 2H), 6.95 (d, J = 6.1 Hz, 1H), 7.29 - 7.59 (m, 7H), 8.07 (d, J = 6.1 Hz, 1H), 8.35 (d, J = 5.3 Hz, 1H), 8.48 (s, 1H), 8.58 (s, 1H)

Example 61: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2,4-difluorophenyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (214 mg) was dissolved in chloroform (5 ml), and 2,4-difluorophenyl isocyanate (180 μl) was then added to the solution. The mixture was allowed to react at 70°C for 4 hr, and a large amount of ether was added to the reaction solution. The resultant precipitate was collected by suction filtration to give 146 mg (yield 46%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 3.99 (s, 3H), 7.03 - 7.10 (m, 1H), 7.28 - 7.37 (m, 2H), 7.40 (s, 1H), 7.56 (s, 2H), 8.08 - 8.21 (m, 2H), 8.57 (s, 1H), 8.80 (s, 1H), 9.30 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 487, 489 (M^++1)

Example 62: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (5.13 g) was dissolved in chloroform (100 ml) and triethylamine (50 ml), and a solution of triphosgene (4.59 g) in chloroform (3 ml) was then added to the solution. The mixture was stirred for 30 min. Next, n-propylamine (2.74 g) was added to the reaction solution, and the mixture was stirred for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (50/1) to give 4.14 g (yield 64%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz,

3H), 1.41 - 1.53 (m, 2H), 3.05 - 3.12 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.99 (t, J = 5.4 Hz, 1H), 7.22 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.38 (s, 1H), 7.46 (d, J = 2.9 Hz, 1H), 7.54 (s, 1H), 8.04 (s, 1H), 8.20 (d, J = 9.3 Hz, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 417 (M^++1)

Example 63: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-ethylurea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, ethylamine hydrochloride (69 mg) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the solution was purified by HPLC by development with chloroform/methanol to give 10 mg (yield 16%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.07 (t, J = 7.3 Hz, 3H), 3.11 - 3.14 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.10 (t, J = 5.4 Hz, 1H), 7.14 (d, J = 9.0 Hz, 2H), 7.37 (s, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 8.49 (br, 1H), 8.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 369 (M^++1)

Example 64: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, propylamine (21 μl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the solution was purified by HPLC by development with chloroform/methanol to give 30 mg (yield 47%) of

the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, J = 7.6 Hz, 3H), 1.41 - 1.50 (m, 2H), 3.04 - 3.08 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.15 (t, J = 5.9 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.37 (s, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 8.48 (br, 1H), 8.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 383 (M^++1)

Example 65: N-Butyl-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, butylamine (22 μl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 29 mg (yield 43%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.28 - 1.47 (m, 4H), 3.07 - 3.12 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.12 (t, J = 5.6 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.37 (s, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 8.47 (br, 1H), 8.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 397 (M^++1)

Example 66: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-pentylurea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solutioin of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, amylamine (26 μl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with

chloroform/methanol to give 21 mg (yield 30%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, J = 7.1 Hz, 3H), 1.27 - 1.47 (m, 4H), 1.41 - 1.48 (m, 2H), 3.06 - 3.11 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.13 (t, J = 5.6 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.37 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.55 (s, 1H), 8.47 (br, 1H), 8.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 411 (M^++1)

Example 67: N-(sec-Butyl)-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, sec-butylamine (23 µl) was added, and the mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 33 mg (yield 49%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.88 (t, J = 7.3 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.40 - 1.47 (m, 2H), 3.58 - 3.64 (m, 1H), 3.97 (s, 3H), 3.99 (s, 3H), 5.98 (t, J = 8.1 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.37 (s, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 8.38 (s, 1H), 8.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 397 (M^++1)

Example 68: N-Allyl-N'-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, allylamine hydrochloride (31 mg) was added to the reaction solution, and the mixture was stirred at room

temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 21 mg (yield 33%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.73 - 3.76 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 5.07 - 5.21 (m, 2H), 5.84 - 5.92 (m, 1H), 6.28 (t, J = 5.6 Hz, 1H), 7.16 (d, J = 9.0 Hz, 2H), 7.38 (s, 1H), 7.47 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 8.53 (s, 1H), 8.59 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 381 (M^++1)

Example 69: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-(2-propynyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, propargylamine hydrochloride (31 mg) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 26 mg (yield 41%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.11 - 3.12 (m, 1H), 3.89 - 3.90 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.49 (t, J = 5.9 Hz, 1H), 7.17 (d, J = 9.0 Hz, 2H), 7.38 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.55 (s, 1H), 8.53 (s, 1H), 8.68 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 379 (M^++1)

Example 70: N-(2,4-Difluorobenzyl)-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2,4-difluorobenzylamine (22 μl) was added to the reaction

solution, and the mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 32 mg (yield 41%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.97 (s, 3H), 3.98 (s, 3H), 4.32 - 4.33 (m, 2H), 6.66 (t, J = 5.9 Hz, 1H), 7.06 - 7.10 (m, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.19 - 7.24 (m, 1H), 7.37 (s, 1H), 7.40 - 7.44 (m, 1H), 7.48 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 8.52 (s, 1H), 8.69 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 467 (M^++1)

Example 71: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-(2-pyridylmethyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2,4-difluorobenzylamine (31 µl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 31 mg (yield 43%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.42 (s, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 7.16 - 7.19 (m, 2H), 7.22 - 7.27 (m, 3H), 7.38 (s, 1H), 7.57 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.88 - 7.92 (m, 1H), 8.46 - 8.48 (m, 1H), 8.54 (s, 1H), 8.87 (s, 1H), 12.19 (s, 1H)

Mass analysis, found (FD-MS, m/z): 431 (M^+)

Example 72: N-(2,4-Difluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml), and 2,4-difluorophenyl isocyanate (24 µl) was then added to the solution. The mixture was heated under reflux overnight. The precipitated crystal was collected by filtration and

was washed to give 55 mg (yield 72%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 3.99 (s, 3H), 7.04 - 7.08 (m, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.29 - 7.35 (m, 1H), 7.38 (s, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.56 (s, 1H), 8.06 - 8.14 (m, 1H), 8.51 - 8.54 (m, 1H), 8.54 (s, 1H), 9.11 - 9.12 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 453 (M^++1)

Example 73: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-(4-fluorophenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml), and p-fluorophenyl isocyanate (23 µl) was then added to the solution. The mixture was heated under reflux overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 26 mg (yield 36%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 3.99 (s, 3H), 7.11 - 7.15 (m, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.38 (s, 1H), 7.46 - 7.50 (m, 2H), 7.54 (d, J = 9.0 Hz, 2H), 7.56 (s, 1H), 8.54 (s, 1H), 8.72 (s, 1H), 8.75 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 435 (M^++1)

Example 74: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-(2-methylphenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml), and o-toluyl isocyanate (25 µl) was then added to the solution. The mixture was heated under reflux overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 30 mg (yield 41%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.26 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.93 - 6.98 (m, 1H), 7.13 - 7.19 (m, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.38 (s, 1H), 7.54 - 7.56 (m, 3H), 7.83 - 7.86 (m, 1H), 7.93 (s, 1H), 8.54 (s, 1H), 9.10 - 9.11 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 431 (M^++1)

Example 75: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-(2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (50 mg) was dissolved in chloroform (3 ml), and 2-methoxyphenyl isocyanate (27 μl) was then added to the solution. The mixture was heated under reflux overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 34 mg (yield 45%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.89 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.89 - 7.05 (m, 3H), 7.22 (d, J = 8.8 Hz, 2H), 7.38 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.56 (s, 1H), 8.13 - 8.15 (m, 1H), 8.23 - 8.24 (m, 1H), 8.54 (s, 1H), 9.40 - 9.41 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 447 (M^++1)

Example 76: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-ethylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (200 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (179 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, ethylamine hydrochloride (246 mg) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 159 mg (yield 65%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, J = 7.1 Hz, 3H), 3.11 - 3.16 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.96 (t, J = 5.6 Hz, 1H), 7.23 (dd, J = 2.7 Hz, 9.0 Hz,

1H), 7.39 (s, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.55 (s, 1H), 8.02 (s, 1H), 8.20 (d, J = 9.3 Hz, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 403 (M^++1)

Example 77: N-Butyl-N'-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, butylamine (22 μl) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 30 mg (yield 46%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.31 - 1.46 (m, 4H), 3.09 - 3.14 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.96 (t, J = 5.6 Hz, 1H), 7.23 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.39 (s, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.55 (s, 1H), 8.03 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 431 (M^++1)

Example 78: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-pentylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, amylamine (26 μl) was added to the reaction solution, and the mixture was stirred at room temperature for

additional 30 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 33 mg (yield 49%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.90 (t, J = 7.1 Hz, 3H), 1.24 - 1.34 (m, 4H), 1.43 - 1.48 (m, 2H), 3.08 - 3.14 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.97 (t, J = 5.1 Hz, 1H), 7.23 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.39 (s, 1H), 7.47 (d, J = 2.8 Hz, 1H), 7.55 (s, 1H), 8.03 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 445 (M^++1)

Example 79: N-(sec-Butyl)-N'-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, sec-butylamine (23 μl) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 34 mg (yield 52%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, J = 7.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.43 - 1.46 (m, 2H), 3.58 - 3.66 (m, 1H), 3.97 (s, 3H), 3.99 (s, 3H), 6.88 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 2.4 Hz, 9.3 Hz, 1H), 7.39 (s, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.55 (s, 1H), 7.98 (s,

1H), 8.23 (d, J = 9.0 Hz, 1H), 8.55 - 8.56 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 431 (M^++1)

Example 80: N-Allyl-N'-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, allylamine hydrochloride (21 mg) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 45 mg (yield 72%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.76 - 3.79 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 5.10 - 5.24 (m, 2H), 5.85 - 5.94 (m, 1H), 7.11 (t, J = 5.4 Hz, 1H), 7.24 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.39 (s, 1H), 7.49 (d, J = 2.7 Hz, 1H), 7.55 (s, 1H), 8.14 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 415 (M^++1)

Example 81: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2-propynyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, propargylamine hydrochloride (21 mg) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. The precipitated crystal was collected by filtration and was washed to

give 38 mg (yield 61%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.16 - 3.17 (m, 1H), 3.93 - 3.95 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 7.25 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.30 (t, J = 5.6 Hz, 1H), 7.39 (s, 1H), 7.50 (d, J = 2.7 Hz, 1H), 7.55 (s, 1H), 8.16 (d, J = 9.3 Hz, 1H), 8.18 (s, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 413 (M^++1)

Example 82: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2,4-difluorobenzyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2,4-difluorobenzylamine (22 μl) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. The precipitated crystal was collected by filtration and was washed to give 48 mg (yield 64%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.97 (s, 3H), 3.99 (s, 3H), 4.33 - 4.36 (m, 2H), 7.08 - 7.12 (m, 1H), 7.22 - 7.28 (m, 2H), 7.39 (s, 1H), 7.42 - 7.46 (m, 1H), 7.49 (d, J = 2.7 Hz, 1H), 7.54 (s, 1H), 8.18 - 8.20 (m, 2H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 501 (M^++1)

Example 83: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2-pyridylmethyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-(methylamino)pyridine (19 μl) was added to the reaction solution, and the mixture was stirred at 60°C for additional one hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform.

The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 26 mg (yield 37%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.51 (s, 2H), 4.07 (s, 3H), 4.07 (s, 3H), 7.03 - 7.10 (m, 2H), 7.19 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.35 (s, 1H), 7.36 (d, J = 2.7 Hz, 1H), 7.54 (s, 1H), 7.76 - 7.81 (m, 1H), 8.38 - 8.43 (m, 1H), 8.56 (d, J = 9.0 Hz, 1H), 8.64 (s, 1H), 13.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 466 (M^++1)

<u>Example 85: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(4-fluorophenyl)urea</u>

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml), and p-fluorophenyl isocyanate (21 μl) was then added to the solution. The mixture was stirred at 60°C for one hr. The precipitated crystal was collected by filtration and was washed to give 57 mg (yield 81%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 3.99 (s, 3H), 7.13 - 7.17 (m, 2H), 7.30 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.40 (s, 1H), 7.48 - 7.51 (m, 2H), 7.55 - 7.56 (m, 2H), 8.21 (d, J = 9.0 Hz, 1H), 8.31 (s, 1H), 8.57 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 469 (M^++1)

<u>Example 86: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2-methoxyphenyl)urea</u>

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml), and 2-methoxyphenyl isocyanate (24 μl) was then added to the solution. The mixture was stirred at 60°C for one hr. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 39 mg (yield 54%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.90 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.89 - 7.05 (m, 3H), 7.29 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.40 (s, 1H), 7.54 (d, J = 2.7 Hz, 1H), 7.56 (s, 1H), 8.09 - 8.16 (m, 2H), 8.58 (s, 1H), 8.96 - 9.02 (m, 2H)

Mass analysis, found (ESI-MS, m/z): 418 (M^++1)

Example 87: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(5-chloro-2-pyridyl)urea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (45 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-chloropyridine (23 mg) was added to the reaction solution, and the mixture was stirred at 60°C for additional one hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 39 mg (yield 53%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 4.00 (s, 3H), 7.33 (dd, J = 2.7 Hz, 9.3 Hz, 1H), 7.40 (s, 1H), 7.43 - 7.48 (m, 1H), 7.56 (s, 1H), 7.60 (d, J = 2.7 Hz, 1H), 7.91 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 8.35 (d, J = 8.8 Hz, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.58 (s, 1H), 10.17 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 486 (M^++1)

Example 88: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoro-aniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (47 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min.

Next, propylamine (20 μl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 9 mg (yield 14%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.90 (t, J = 7.6 Hz, 3H), 1.43 - 1.49 (m, 2H), 3.05 - 3.10 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.61 (t, J = 5.6 Hz, 1H), 7.05 - 7.07 (m, 1H), 7.27 - 7.31 (m, 1H), 7.38 (s, 1H), 7.54 (s, 1H), 8.14 - 8.19 (m, 1H), 8.28 - 8.29 (m, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 401 (M^++1)

Example 89: N-Butyl-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (47 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, butylamine (24 μl) was added, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 25 mg (yield 38%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.30 - 1.47 (m, 4H), 3.09 - 3.13 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.58 (t, J = 5.6 Hz, 1H), 7.04 - 7.07 (m, 1H), 7.28 - 7.31 (m, 1H), 7.38 (s, 1H), 7.54 (s, 1H), 8.14 - 8.19 (m, 1H), 8.26 - 8.28 (m, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 415 (M^++1)

Example 90: N-(sec-Butyl)-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (47 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min.

Next, sec-butylamine (25 μl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 12 mg (yield 18%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, J = 7.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.39 - 1.48 (m, 2H), 3.58 - 3.64 (m, 1H), 3.97 (s, 3H), 3.99 (s, 3H), 6.51 (d, J = 7.6 Hz, 1H), 7.04 - 7.08 (m, 1H), 7.30 (dd, J = 2.4 Hz, 11.7 Hz, 1H), 7.39 (s, 1H), 7.54 (s, 1H), 8.16 - 8.22 (m, 2H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 415 (M^++1)

Example 91: N-Allyl-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (47 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, allylamine hydrochloride (30 mg) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 18 mg (yield 28%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.75 - 3.79 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 5.08 - 5.22 (m, 2H), 5.84 - 5.94 (m, 1H), 6.72 (t, J = 5.9 Hz, 1H), 7.06 - 7.08 (m, 1H), 7.30 - 7.33 (m, 1H), 7.39 (s, 1H), 7.54 (s, 1H), 8.13 - 8.18 (m, 1H), 8.40 (s, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 399 (M^++1)

Example 92: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}-N'-(2-propynyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene

(47 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, propargylamine hydrochloride (29 mg) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with chloroform to give 21 mg (yield 33%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.15 (t, J = 2.4 Hz, 1H), 3.91 - 3.94 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 7.07 - 7.11 (m, 1H), 7.33 (dd, J = 2.4 Hz, 11.7 Hz, 1H), 7.39 (s, 1H), 7.54 (s, 1H), 8.09 - 8.15 (m, 1H), 8.47 - 8.48 (m, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 397 (M^++1)

Example 93: N-(2,4-Difluorobenzyl)-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (47 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2,4-difluorobenzylamine (28 μl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. The precipitated crystal was collected by filtration and was washed to give 20 mg (yield 26%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.97 (s, 3H), 3.99 (s, 3H), 4.34 (d, J = 5.8 Hz, 2H), 7.07 - 7.11 (m, 3H), 7.21 - 7.27 (m, 1H), 7.30 - 7.33 (m, 1H), 7.39 (s, 1H), 7.41 - 7.47 (m, 1H), 7.54 (s, 1H), 8.12 - 8.16 (m, 1H), 8.46 - 8.47 (m, 1H), 8.55 (s, 1H)

Mass analysis, found (FD-MS, m/z): 484 (M^+)

Example 94: N-(2,4-Difluorophenyl)-N'-{4-[(6,7-

dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml), and 2,4-difluorophenyl isocyanate (29 μl) was then added to the solution. The mixture was stirred at 60°C overnight. The precipitated crystal was collected by filtration and was washed to give 50 mg (yield 67%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 3.99 (s, 3H), 7.04 - 7.08 (m, 1H), 7.13 - 7.15 (m, 1H), 7.29 - 7.40 (m, 3H), 7.55 (s, 1H), 8.10 - 8.23 (m, 2H), 8.57 (s, 1H), 8.97 - 9.04 (m, 2H)

Mass analysis, found (ESI-MS, m/z): 471 (M^++1)

Example 95: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}-N'-(2-methylphenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml), and o-toluyl isocyanate (30 μl) was then added to the solution. The mixture was stirred at 60°C overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 17 mg (yield 24%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.27 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.95 - 6.98 (m, 1H), 7.12 - 7.20 (m, 3H), 7.36 - 7.39 (m, 2H), 7.55 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 8.21 - 8.26 (m, 1H), 8.35 (s, 1H), 8.57 (s, 1H), 9.00 - 9.02 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 449 (M^++1)

Example 96: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluorophenyl}-N'-(2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-fluoroaniline (50 mg) was dissolved in chloroform (3 ml), and 2-methoxyphenyl isocyanate (32 μl) was then added to the solution. The mixture was stirred at 60°C overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with

chloroform/methanol to give 22 mg (yield 30%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.89 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.88 - 7.04 (m, 3H), 7.11 - 7.14 (m, 1H), 7.35 - 7.39 (m, 1H), 7.40 (s, 1H), 7.56 (s, 1H), 8.12 - 8.15 (m, 1H), 8.19 - 8.25 (m, 1H), 8.57 (s, 1H), 8.75 - 8.78 (m, 1H), 9.26 - 9.29 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 465 (M^++1)

Example 97: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylphenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (48 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, propylamine (20 µl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 30 mg (yield 47%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, J = 7.5 Hz, 3H), 1.41 - 1.50 (m, 2H), 2.03 (s, 3H), 3.03 - 3.08 (m, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 6.13 (t, J = 5.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.28 (dd, J = 2.4 Hz, 8.5 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.38 (s, 1H), 7.58 (s, 1H), 8.39 (s, 1H), 8.50 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 397 (M^++1)

Example 98: N-Butyl-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-3-methylphenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (48 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, butylamine (24 µl) was added to the reaction solution, and the mixture was further stirred at room

temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 31 mg (yield 47%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.29 - 1.46 (m, 4H), 2.03 (s, 3H), 3.07 - 3.12 (m, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 6.11 (t, J = 5.6 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.27 (dd, J = 2.3 Hz, 8.5 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.38 (s, 1H), 7.58 (s, 1H), 8.39 (s, 1H), 8.51 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 411 (M^++1)

Example 99: N-(2,4-Difluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-3-methylphenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylaniline (50 mg) was dissolved in chloroform (3 ml), and 2,4-difluorophenyl isocyanate (23 μl) was then added to the solution. The mixture was heated under reflux overnight. The precipitated crystal was collected by filtration and was washed to give 59 mg (yield 79%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.07 (s, 3H), 3.99 (s, 3H), 3.99 (s, 3H), 7.03 - 7.08 (m, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.29 - 7.37 (m, 2H), 7.39 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.60 (s, 1H), 8.07 - 8.14 (m, 1H), 8.52 (s, 1H), 9.03 - 9.05 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 467 (M^++1)

Example 100: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylphenyl}-N'-(4-fluorophenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylaniline (50 mg) was dissolved in chloroform (3 ml), and p-fluorophenyl isocyanate (22 μl) was then added to the solution. The mixture was heated under reflux overnight. The precipitated crystal was collected by filtration and was washed to give 42 mg (yield 58%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.07 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 7.10 - 7.14 (m, 3H), 7.35 (dd, J =

2.4 Hz, 8.5 Hz, 1H), 7.39 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.46 - 7.49 (m, 2H), 7.59 (s, 1H), 8.51 (s, 1H), 8.66 (s, 1H), 8.70 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 449 (M^++1)

Example 101: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylphenyl}-N'-(2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-3-methylaniline (50 mg) was dissolved in chloroform (3 ml), and 2-methoxyphenyl isocyanate (26 µl) was then added to the solution. The mixture was heated under reflux overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 41 mg (yield 55%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.07 (s, 3H), 3.89 (s, 3H), 3.99 (s, 3H), 3.99 (s, 3H), 6.88 - 6.97 (m, 2H), 7.01 - 7.03 (m, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 2.4 Hz, 8.5 Hz, 1H), 7.39 (s, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.60 (s, 1H), 8.13 - 8.15 (m, 1H), 8.23 (s, 1H), 8.52 (s, 1H), 9.33 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 461 (M^++1)

Example 102: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylphenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (48 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, propylamine (20 µl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 30 mg (yield 47%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.90 (t, J = 7.3 Hz, 3H), 1.42 - 1.51 (m, 2H), 2.21 (s, 3H), 3.04 - 3.09 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.53 (t, J = 5.6 Hz,

1H), 7.02 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 7.54 (s, 1H), 7.65 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 8.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 397 (M^++1)

Example 103: N-Butyl-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-2-methylphenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylaniline (50 mg) was dissolved in chloroform (3 ml) and triethylamine (0.2 ml), and a solution of triphosgene (48 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, butylamine (24 μl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 37 mg (yield 56%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.92 (t, J = 7.1 Hz, 3H), 1.31 - 1.48 (m, 4H), 2.21 (s, 3H), 3.08 - 3.13 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.50 (t, J = 5.4 Hz, 1H), 7.02 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 7.54 (s, 1H), 7.64 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 8.53 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 411 (M^++1)

Example 104: N-(2,4-Difluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-2-methylphenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylaniline (50 mg) was dissolved in chloroform (3 ml), and 2,4-difluorophenyl isocyanate (23 μl) was then added to the solution. The mixture was heated under reflux overnight. The precipitated crystal was collected by filtration and was washed to quantitatively give the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.29 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 7.03 - 7.11 (m, 2H), 7.16 (d, J = 2.7 Hz, 1H), 7.29 - 7.35 (m, 1H), 7.38 (s, 1H), 7.55 (s, 1H), 7.87 - 7.90 (m, 1H), 8.13 - 8.19 (m, 1H), 8.36 - 8.39 (m,

1H), 8.55 (s, 1H), 8.92 - 8.95 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 467 (M^++1)

Example 105: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylphenyl}-N'-(4-fluorophenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylaniline (50 mg) was dissolved in chloroform (3 ml), and p-fluorophenyl isocyanate (22 μl) was then added to the solution. The mixture was heated under reflux overnight. The precipitated crystal was collected by filtration and was washed to quantitatively give the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.28 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 7.08 - 7.15 (m, 4H), 7.38 (s, 1H), 7.47 - 7.50 (m, 2H), 7.55 (s, 1H), 7.84 - 7.88 (m, 1H), 7.98 (s, 1H), 8.55 (s, 1H), 9.03 - 9.05 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 449 (M^++1)

Example 106: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylphenyl}-N'-(2-methoxyphenyl)urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-methylaniline (50 mg) was dissolved in chloroform (3 ml), and 2-methoxyphenyl isocyanate (26 μl) was then added to the solution. The mixture was heated under reflux overnight. The precipitated crystal was collected by filtration and was washed to give 70 mg (yield 95%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.29 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.87 - 6.97 (m, 2H), 7.02 - 7.04 (m, 1H), 7.08 (dd, J = 2.9 Hz, 8.8 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.38 (s, 1H), 7.55 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 8.13 - 8.15 (m, 1H), 8.55 (s, 1H), 8.58 (s, 1H), 8.61 - 8.62 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 461 (M^++1)

Example 107: N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-nitrophenyl}-N'-propylurea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-nitroaniline (50 mg) was dissolved in chloroform (10 ml) and triethylamine (0.2 ml), and a solution of triphosgene (43 mg) in chloroform was then added to the solution.

The mixture was stirred at room temperature for 30 min. Next, propylamine (18 µl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 24 mg (yield 38%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.45 - 1.51 (m, 2H), 3.06 - 3.09 (m, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 7.40 (s, 1H), 7.52 (br, 1H), 7.58 (s, 1H), 7.67 - 7.70 (m, 1H), 8.04 - 8.06 (m, 1H), 8.38 - 8.41 (m, 1H), 8.57 (s, 1H), 9.35 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 428 (M^++1)

Example 108: N-Butyl-N'-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-2-nitrophenyl}urea

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]-2-nitroaniline (50 mg) was dissolved in chloroform (10 ml) and triethylamine (0.2 ml), and a solution of triphosgene (43 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, butylamine (22 µl) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 15 mg (yield 23%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.30 - 1.49 (m, 4H), 3.10 - 3.15 (m, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 7.40 (s, 1H), 7.51 (br, 1H), 7.57 (s, 1H), 7.68 (dd, J = 2.9 Hz, 9.3 Hz, 1H), 8.05 (d, J = 2.9 Hz, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.57 (s, 1H), 9.35 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 442 (M^++1)

Example 109: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N-methoxymethyl-N'-propylurea

N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-propylurea (100 mg) was dissolved in

anhydrous tetrahydrofuran (30 ml), and sodium hydride (60 wt%, 88 mg) was added to the solution. The mixture was stirred at room temperature for 15 min. Next, chloromethyl methyl ether (67 μl) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. The solvent was removed by distillation under the reduced pressure, and water was added to the residue. The mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 18 mg (yield 18%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, J = 7.6 Hz, 3H), 1.46 - 1.55 (m, 2H), 3.20 (br, 2H), 3.48 (s, 3H), 4.07 (s, 3H), 4.08 (s, 3H), 4.54 (br, 2H), 7.29 (dd, J = 2.7 Hz, 8.5 Hz, 1H), 7.37 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.50 (d, J = 2.7 Hz, 1H), 8.66 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 461 (M^++1)

Example 110: N-Acetyl-N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea

N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-phenyl}-N'-propylurea (100 mg) was dissolved in anhydrous tetrahydrofuran (30 ml), and sodium hydride (60 wt%, 88 mg) was added to the solution. The mixture was stirred at room temperature for 15 min. Next, acetyl chloride (63 μl) was added to the reaction solution, and the mixture was stirred at room temperature for additional 2 hr. The solvent was removed by distillation under the reduced pressure, and water was added to the residue. The mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/acetone to give 27 mg (yield

26%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.98 (t, J = 7.3 Hz, 3H), 1.59 - 1.68 (m, 2H), 2.04 (s, 3H), 3.27 - 3.36 (m, 2H), 4.07 (s, 3H), 4.08 (s, 3H), 7.31 - 7.33 (m, 1H), 7.35 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.50 - 7.51 (m, 2H), 8.63 (s, 1H), 9.08 (br, 1H)

Mass analysis, found (ESI-MS, m/z): 459 (M^++1)

Example 111: N'-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N-methyl-N-propylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (56 mg) was dissolved in chloroform (4 ml) and triethylamine (0.3 ml), and a solution of triphosgene (50 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, N-methylpropylamine (26 μl) was added to the reaction solution, and the mixture was stirred at room temperature for additional one hr. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol. The solvent was removed by distillation, and the resultant crystal was washed with hexane to give 42 mg (yield 58%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.99 (t, J = 7.3 Hz, 3H), 1.64 - 1.74 (m, 2H), 3.08 (s, 3H), 3.34 (t, J = 7.6 Hz, 2H), 4.07 (s, 3H), 4.08 (s, 3H), 7.00 (s, 1H), 7.17 (dd, J = 2.7 Hz, 9.3 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.38 (s, 1H), 7.53 (s, 1H), 8.41 (d, J = 9.0 Hz, 1H), 8.64 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 431 (M^++1)

Example 112: N'-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N-ethyl-N-propylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (80 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (72 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 15 min. Next, N-ethylpropylamine (44 μl) was added to the

reaction solution, and the mixture was stirred at room temperature for additional 30 min. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol. The solvent was removed by distillation. The resultant crystal was washed with hexane to give 40 mg (yield 37%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.00 (t, J = 7.3 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.69 - 1.74 (m, 2H), 3.32 (t, J = 7.6 Hz, 2H), 3.43 (q, J = 7.1 Hz, 2H), 4.07 (s, 3H), 4.07 (s, 3H), 7.02 (s, 1H), 7.17 (dd, J = 2.9 Hz, 9.2 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.36 (s, 1H), 7.53 (s, 1H), 8.42 (d, J = 9.0 Hz, 1H), 8.63 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 445 (M^++1)

Example 113: N'-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N,N-dipropylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (100 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (90 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 15 min. Next, dipropylamine (62 µl) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol. The solvent was removed by distillation, and the resultant crystal was washed with hexane to give 48 mg (yield 35%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.99 (t, J = 7.3 Hz, 6H), 1.66 - 1.76 (m, 4H), 3.32 (t, J = 7.8 Hz, 4H), 4.07 (s, 3H), 4.07 (s, 3H), 7.03 (s, 1H), 7.16 (dd, J = 2.7 Hz, 9.3 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.34 (s, 1H), 7.52 (s, 1H), 8.43 (d, J = 9.0 Hz, 1H), 8.63 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 459 (M^++1)

Example 114: N-Butyl-N'-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N-methylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (80 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (72 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 15 min. Next, N-methylbutylamine (43 µl) was added to the reaction solution, and the mixture was stirred at room temperature for additional 30 min. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol. The solvent was removed by distillation, and the resultant crystal was washed with hexane to give 26 mg (yield 24%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.99 (t, J = 7.3 Hz, 3H), 1.38 - 1.43 (m, 2H), 1.62 - 1.66 (m, 2H), 3.07 (s, 3H), 3.40 (t, J = 7.3 Hz, 2H), 4.07 (s, 3H), 4.07 (s, 3H), 7.00 (s, 1H), 7.17 (dd, J = 2.7 Hz, 9.3 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.36 (s, 1H), 7.53 (s, 1H), 8.41 (d, J = 9.3 Hz, 1H), 8.63 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 445 (M^++1)

Example 115: N'-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N-(4-chlorophenyl)-N-methylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (80 mg) was dissolved in chloroform (3 ml) and triethylamine (0.3 ml), and a solution of triphosgene (72 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 15 min. Next, 4-chloro-N-methylaniline (35 µl) was added to the reaction solution, and the mixture was heated under reflux for additional 30 min. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol, and the solvent was removed by distillation. The resultant crystal was washed with ether to give 83 mg (yield 69%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.36 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.89 (s, 1H), 7.17 (dd, J = 2.7 Hz,

9.0 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.33 - 7.35 (m, 3H), 7.48 - 7.50 (m, 3H), 8.41 (d, J = 9.0 Hz, 1H), 8.61 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 499 (M^++1)

Example 116: N'-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N,N-diethylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (2 ml) and triethylamine (0.5 ml), and a solution of triphosgene (48 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, diethylamine (0.5 ml) was added to the reaction solution, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 37 mg (yield 93%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (t, J = 7.1 Hz, 6H), 3.44 (q, J = 7.1 Hz, 4H), 4.12 (s, 3H), 4.20 (s, 3H), 7.16 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.27 (s, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.59 (s, 1H), 8.15 (s, 1H), 8.48 (d, J = 9.0 Hz, 1H), 8.81 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 431 (M^++1)

Example 117: N-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-methylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (2 ml) and triethylamine (0.5 ml), and a solution of triphosgene (48 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, the reaction solution was cooled to -78°C, and methylamine hydrochloride (130 mg) was added to the cooled reaction solution. The temperature of the mixture was spontaneously raised, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol

to give 41 mg (yield 70%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.68 (d, J = 4.4 Hz, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 6.86 - 6.88 (m, 1H), 7.21 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.37 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.53 (s, 1H), 8.07 (s, 1H), 8.17 (d, J = 9.0 Hz, 1H), 8.54 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 389 (M^++1)

Example 118: N'-{2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N,N-dimethylurea

2-Chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]-aniline (50 mg) was dissolved in chloroform (2 ml) and triethylamine (0.5 ml), and a solution of triphosgene (48 mg) in chloroform was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, the reaction solution was cooled to -78°C, and dimethylamine hydrochloride (250 mg) was added to the cooled reaction solution. The temperature of the mixture was spontaneously raised, and the mixture was further stirred at room temperature overnight. Methanol was added to the reaction solution, and the mixture was purified by HPLC by development with chloroform/methanol to give 33 mg (yield 53%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.11 (s, 6H), 4.12 (s, 3H), 4.20 (s, 3H), 7.05 (s, 1H), 7.17 (dd, J = 2.4 Hz, 9.3 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.59 (s, 1H), 8.15 (s, 1H), 8.46 (d, J = 9.3 Hz, 1H), 8.82 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 403 (M^++1)

Example 119: N-(2-Chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (75 mg), potassium carbonate (51 mg), and 1,3-dibromopropane (76 μl) was dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the

mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 74 mg (yield 78%) of N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]-oxy}-2-chlorophenyl)-N'-propylurea as an intermediate. The intermediate (74 mg), potassium carbonate (51 mg), and morpholine (130 μl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 49 mg (yield 63%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J = 7.44 Hz, 3H), 1.41 - 1.50 (m, 2H), 1.97 (t, J = 6.83 Hz, 1H), 2.33 - 2.49 (m, 4H), 3.04 - 3.09 (m, 2H), 3.32 - 3.38 (m, 4H), 3.52 - 3.68 (m, 3H), 4.03 (s, 3H), 4.23 - 4.29 (m, 1H), 4.32 (t, J = 5.89 Hz, 1H), 6.98 (t, J = 5.49 Hz, 1H), 7.21 (dd, J = 2.68, 9.03 Hz, 1H), 7.36 (s, 1H), 7.46 (d, J = 2.68 Hz, 1H), 7.53 (d, J = 7.81 Hz, 1H), 8.03 (s, 1H), 8.18 (d, J = 9.27 Hz, 1H), 8.54 (d, J = 4.39 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 529 (M^+)

Example 120: N-(2-Chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (72 mg), potassium carbonate (30 mg), and 1,2-dibromoethane (62 μl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 3 hr. The

solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 40 mg (yield 45%) of N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinazolinyl]-oxy}-2-chlorophenyl)-N'-propylurea as an intermediate. The intermediate (45 mg), potassium carbonate (30 mg), and morpholine (80 µl) were dissolved in N,N-dimethylformamide (2 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 42 mg (yield 56%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J = 7.32 Hz, 3H), 1.43 - 1.49 (m, 2H), 2.32 - 2.38 (m, 2H), 2.66 (bs, 1H), 2.79 (t, J = 5.86 Hz, 1H), 3.04 - 3.09 (m, 2H), 3.29 - 3.36 (m, 4H), 3.53 (m, 1H), 3.57 - 3.59 (m, 2H), 3.96 (s, 3H), 4.31 (t, J = 5.85 Hz, 1H), 6.98 (m, 1H), 7.21 - 7.23 (m, 1H), 7.41 (s, 1H), 7.46 - 7.47 (m, 1H), 7.55 (d, J = 12.69 Hz, 1H), 8.03 (s, 1H), 8.19 (d, J = 9.27 Hz, 1H), 8.55 (d, J = 5.37 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 517 (M^++1)

Example 121: N-(2-Chloro-4-{[7-(3-hydroxypropoxy)-6-methoxy-4-quinazolinyl]oxy}phenyl)-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (55 mg), potassium carbonate (20 mg), and 3-bromo-1-propanol (62 µl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 3 hr. The

solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 25 mg (yield 40%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.44 Hz, 3H), 1.24 (bs, 1H), 1.43 - 1.52 (m, 2H), 1.97 (t, J = 6.22 Hz, 2H), 3.06 - 3.11 (m, 2H), 3.56 - 3.71 (m, 2H), 3.97 (s, 3H), 4.27 (m, 2H), 6.99 (t, J = 5.62 Hz, 1H), 7.23 (dd, J = 2.68, 9.03 Hz, 1H), 7.38 (d, J = 9.03 Hz, 1H), 7.47 (d, J = 2.68 Hz, 1H), 7.54 (s, 1H), 8.05 (s, 1H), 8.20 (d, J = 9.03 Hz, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 461 (M^++1)

Example 122: N-(2-Chloro-4-{[7-(2-hydroxyethoxy)-6-methoxy-4-quinazolinyl]oxy}phenyl)-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (50 mg), potassium carbonate (30 mg), and ethylenebromohydrin (44 µl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 12 mg (yield 22%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.44 Hz, 3H), 1.42 - 1.49 (m, 2H), 3.06 - 3.11 (m, 2H), 3.80 - 3.83 (m, 2H), 3.98 (s, 3H), 4.22 (t, J = 4.64 Hz, 2H), 4.98 (t, J = 5.37 Hz, 1H), 6.99 (t, J = 5.37 Hz, 1H), 7.33 (dd, J = 2.69 Hz, 9.03 Hz, 1H), 7.39 (s, 1H), 7.48 (d, J = 2.68 Hz, 1H), 7.55 (s, 1H), 8.05 (s, 1H), 8.19 (d, J = 9.27

Hz, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 447 (M^++1)

Example 123: N-(2-Chloro-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 4-chloromethylpyridine hydrochloride (41 mg), were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, followed by extraction with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 65 mg (yield 66%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J = 7.6 Hz, 3H), 1.53 - 1.64 (m, 2H), 3.25 (dd, J = 7.3 Hz, 12.9 Hz, 2H), 4.07 (s, 3H), 5.32 (s, 2H), 6.66 (s, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.27 (s, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.41 (d, J = 5.9 Hz, 2H), 7.54 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.59 (s, 1H), 8.63 (d, J = 6.1 Hz, 2H)

Mass analysis, found (ESI-MS, m/z): 494 (M^++1)

Example 124: N-[2-Chloro-4-({6-methoxy-7-[(5-morpholinopentyl)oxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (70 mg), potassium carbonate (30 mg), and pentamethylene bromide (80 μl) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 43 mg (yield 46%) of N-[4-({7-(5-bromopentyl)oxy}-6-methoxy-4-

quinazolinyl)oxy]-2-chlorophenyl]-N'-propylurea as an intermediate. The intermediate (43 mg), potassium carbonate (30 mg), and morpholine (70 μl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 30 mg (yield 68%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.71 (t, J = 7.32 Hz, 3H), 2.28 (t, J = 7.20 Hz, 2H), 2.63 (m, 2H), 3.08 - 3.14 (m, 5H), 3.29 - 3.30 (m, 5H), 3.47 (bs, 1H), 3.73 (m, 1H), 3.86 - 3.90 (m, 2H), 4.36 (t, J = 4.65 Hz, 3H), 4.46 (t, J = 4.76 Hz, 1H), 4.77 (s, 1H), 4.99 (t, J = 6.34 Hz, 2H), 7.80 (m, 1H), 8.02 (dd, J = 2.68 Hz, 9.27 Hz, 1H), 8.18 (s, 1H), 8.27 (d, J = 2.68 Hz, 1H), 8.34 (s, 1H), 8.85 (s, 1H), 9.00 (d, J = 9.03 Hz, 1H), 9.35 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 559 (M^++1)

Example 125: N-{2-Chloro-4-[(6-methoxy-7-{[5-(1*H*-1,2,3-triazol-1-yl)pentyl]oxy}-4-quinazolinyl)oxy]phenyl}-N'-propylurea

Triazole (0.41 ml), 1-bromo-5-chloropentane (1.0 ml), tetrabutylammonium iodide (10 mg), and a 3 M aqueous sodium hydroxide solution (1 ml) were dissolved in acetone (10 ml), and the solution was stirred at 50°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography by development with chloroform to give an intermediate (390 mg).

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and the above intermediate (52 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 120°C for 5 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 41 mg (yield 38%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J = 7.6 Hz, 3H), 1.50 - 1.65 (m, 4H), 1.90 - 2.08 (m, 4H), 3.24 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 4.01 (s, 3H), 4.17 (t, J = 6.6 Hz, 2H), 4.44 (t, J = 7.3 Hz, 2H), 4.88 - 4.94 (m, 1H), 6.32 (s, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.25 (s, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.48 (s, 1H), 7.55 (s, 1H), 7.70 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.58 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 540 (M^++1)

Example 126: N'-(2-Chloro-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinazolinyl]oxy}phenyl)-N,N-diethylurea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-diethylurea, 83 mg), potassium carbonate (138 mg), and 4-chloromethylpyridine hydrochloride (49 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 57 mg (yield 56%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, J = 7.3 Hz, 6H), 3.41 (q, J = 7.1 Hz, 4H), 4.08 (s, 3H), 5.32 (s, 2H), 6.98 (s, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.27 (s,

1H), 7.29 (d, J = 2.7 Hz, 1H), 7.41 (d, J = 5.9 Hz, 2H), 7.55 (s, 1H), 8.37 (d, J = 9.0 Hz, 1H), 8.58 (s, 1H), 8.63 (d, J = 5.9 Hz, 2H)

Mass analysis, found (ESI-MS, m/z): 508 (M^++1)

Example 127: N-(2-Chloro-4-{[6-methoxy-7-(4-morpholinobutoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (70 mg), potassium carbonate (30 mg), and pentamethylene bromide (80 µl) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 43 mg (yield 46%) of N-(4-{[7-(4-bromobutoxy)-6-methoxy-4-quinazolinyl]-oxy}-2-chlorophenyl)-N'-propylurea as an intermediate. The intermediate (43 mg), potassium carbonate (30 mg), and morpholine (40 µl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 23 mg (yield 53%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, J = 7.32 Hz, 3H), 1.56 - 1.62 (m, 13H), 2.00 - 2.08 (m, 2H), 3.26 - 3.28 (m, 2H), 4.04 (s, 3H), 4.24 (m, 2H), 4.72 - 4.77 (m, 1H), 6.65 (s, 1H), 6.99 (s, 1H), 7.19 - 7.26 (m, 1H), 7.30 (s,

1H), 7.32 - 7.34 (m, 1H), 7.51 (s, 1H), 8.25 (d, J = 9.03 Hz, 1H), 8.61 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 545 (M^++1)

Example 128: N-[2-Chloro-4-({6-methoxy-7-[2-(4-methylpiperazino)ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (60 mg), potassium carbonate (30 mg), and 1,2-dibromoethane (70 µl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 46 mg (yield 62%) of N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinazolinyl]-oxy}-2-chlorophenyl)-N'-propylurea as an intermediate. The intermediate (46 mg), potassium carbonate (20 mg), and N-methylpiperazine (50 µl) were dissolved in N,N-dimethylformamide (3 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 24 mg (yield 50%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, J = 7.32 Hz, 3H), 1.61 - 1.64 (m, 2H), 2.75 (m, 2H), 3.00 - 3.16 (m, 4H), 3.25 - 3.16 (m, 4H), 3.25 - 3.29 (m, 2H), 4.02 (s, 3H), 4.27 - 4.35 (m, 2H), 4.78 - 4.83 (m, 2H), 5.33 (s, 3H), 6.69 (s, 1H), 7.17 (dd, J = 2.68 Hz, 9.03 Hz, 1H), 7.31

(s, 1H), 7.49 (s, 1H), 8.26 (d, J = 9.27 Hz, 1H), 8.59 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 530 (M^++1)

Example 129: N-{2-Chloro-4-[(7-{2-[(2-hydroxyethyl)-(methyl)amino]ethoxy}-6-methoxy-4-quinazolinyl)oxy]-phenyl}-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (65 mg), potassium carbonate (30 mg), and 1,2-dibromoethane (30 µl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 36 mg (yield 45%) of N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinazolinyl]-oxy}-2-chlorophenyl)-N'-propylurea as an intermediate. The intermediate (36 mg), potassium carbonate (30 mg), and N-methylethanolamine (30 µl) were dissolved in N,N-dimethylformamide (3 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 21 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, J = 7.32 Hz, 3H), 1.59 (m, 2H), 1.94 (bs, 1H), 3.23 (m, 2H), 4.03 (s, 3H), 4.07 - 4.15 (m, 4H), 4.76 (m, 4H), 5.35 (s, 3H), 7.10 - 7.17 (m, 1H), 7.28 (s, 3H), 7.40 (s, 1H), 7.54 (s, 1H), 8.37 (d, J = 9.03 Hz, 1H), 8.64 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 504 (M^++1)

Example 130: N-[2-Chloro-4-({6-methoxy-7-[3-(4-methylpiperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (75 mg), potassium carbonate (30 mg), and 1,3-dibromopropane (75 µl) were dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 50 mg (yield 52%) of N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]-oxy}-2-chlorophenyl)-N'-propylurea as an intermediate. The intermediate (30 mg), potassium carbonate (20 mg), and N-methylpiperazine (40 µl) were dissolved in N,N-dimethylformamide (3 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 20 mg (yield 63%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, J = 7.32 Hz, 3H), 1.58 - 1.62 (m, 2H), 2.25 - 2.50 (m, 3H), 2.70 - 2.85 (m, 3H), 2.92 - 2.98 (m, 3H), 3.25 (m, 2H), 4.04 (s, 3H), 4.25 (m, 2H), 4.83 (m, 3H), 5.34 (s, 3H), 6.70 (s, 1H), 7.21 (dd, J = 2.68, 9.03 Hz, 1H), 7.26 (s, 2H), 7.31 (s, 1H), 7.49 (s, 1H), 8.18 (d, J = 9.27 Hz, 1H), 8.59 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 544 (M^++1)

Example 131: N'-[2-Chloro-4-({6-methoxy-7-[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinazolinyl}oxy)phenyl]-N,N-diethylurea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-diethylurea, 83 mg), potassium carbonate (138 mg), and 2-(1H-1,2,3-triazol-1-yl)ethyl 4-methyl-1-benzenesulfonate (59 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate. Triphosgene (90 mg) was added to a solution of the intermediate and triethylamine (0.027 ml) in chloroform (1 ml) at 0°C, and the mixture was stirred for 30 min. The reaction mixture was cooled to 0°C, and diethylamine (0.044 ml) was then added dropwise to the cooled reaction mixture. The temperature of the mixture was raised to room temperature over a period of 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, followed by extraction with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 30 mg (yield 29%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, J = 7.1 Hz, 6H), 3.41 (q, J = 7.1 Hz, 4H), 4.03 (s, 3H), 4.53 (t, J = 4.9 Hz, 2H), 4.94 (t, J = 5.1 Hz, 2H), 6.98 (s, 1H), 7.13 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.26 (s, 1H), 7.73 (s, 1H), 7.94 (s, 1H), 8.38 (d, J = 9.0 Hz, 1H), 8.60 (s, 1H)

Example 132: 3-{[4-(3-Chloro-4-{[(diethylamino)-carbonyl]amino}phenoxy)-6-methoxy-7-quinazolinyl]oxy}-propyl-N,N-diethylcarbamate

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-diethylurea, 83 mg), potassium carbonate (138 mg), and 3-bromo-1-propanol (0.027 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate. Triphosgene (90 mg) was added to a solution of the intermediate and triethylamine (0.027 ml) in chloroform (1 ml) at 0°C, and the mixture was stirred for 30 min. The reaction mixture was cooled to 0°C, and diethylamine (0.044 ml) was then added dropwise to the cooled reaction mixture. The temperature of the mixture was raised to room temperature over a period of 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 19 mg (yield 17%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.04 (t, J = 7.1 Hz, 6H), 1.22 (t, J = 7.3 Hz, 6H), 3.09 (q, J = 7.1 Hz, 4H), 3.36 (q, J = 7.1 Hz, 4H), 3.75 (t, J = 6.3 Hz, 2H), 3.97 (s, 3H), 4.29 (t, J = 6.1 Hz, 2H), 6.93 (s, 1H), 7.10 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 7.27 (s, 1H), 7.45 (s, 1H), 8.33 (d, J = 9.3 Hz, 1H), 8.55 (s, 1H)

Example 133: N-[2-Chloro-4-({6-methoxy-7-[3-(4-pyridylthio)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propyl-

urea, 80 mg), potassium carbonate (138 mg), and 4-mercaptopyridine (22 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 60 mg (yield 72%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.50 - 1.60 (m, 2H), 2.24 - 2.32 (m, 2H), 3.11 - 3.24 (m, 4H), 3.99 (s, 3H), 4.25 (t, J = 5.9 Hz, 2H), 4.70 - 4.80 (m, 1H), 6.62 (s, 1H), 7.11 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.11 - 7.16 (m, 2H), 7.23 (s, 1H), 7.25 (d, J = 2.7 Hz, 1H), 7.45 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.30 - 8.34 (m, 2H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 554 (M^++1)

Example 134: N-{2-Chloro-4-[(6-methoxy-7-{3-[(1-methyl-1*H*-1,2,3,4-tetrazol-5-yl)thio]propoxy}-4-quinazolinyl)-oxy]phenyl}-N'-propylurea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 5-mercapto-1-tetrazole (23 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 71 mg (yield 85%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.51 - 1.56 (m, 2H), 2.39 - 2.48 (m, 2H), 3.17 - 3.23 (m, 2H), 3.56 (t, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.97 (s, 3H), 4.27 (t, J = 5.9 Hz, 2H), 4.75 - 4.82 (m, 1H), 6.63

(s, 1H), 7.10 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.24 (d, J = 3.7 Hz, 1H), 7.44 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 559 (M^++1)

Example 135: N-(2-Chloro-4-{[6-methoxy-7-(3-piperidinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (500 mg), potassium carbonate (857 mg), and 1,3-dibromopropane (0.5 ml) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform/2-propanol (4/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 451 mg (yield 71%) of N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea. N-(4-{[7-(3-Bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea (70 mg), potassium carbonate (54 mg), and piperidine (39 µl) were dissolved in N,N-dimethylformamide (2 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (20/1) to give 35 mg (yield 50%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, J = 7.6 Hz, 3H), 1.46 (br, 2H), 1.54 - 1.66 (m, 8H), 2.15 (br, 2H), 2.44 (br, 2H), 2.55 (br, 2H), 3.20 - 3.30 (m, 2H), 4.04 (s, 3H), 4.27 (t, J = 6.6 Hz, 2H), 4.77 (t, J = 5.9 Hz, 1H),

6.65 (s, 1H), 7, 17 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.32 (d, J = 2.7 Hz, 1H), 7.33 (s, 1H), 7.49 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.61 (s, 1H)

Example 136: N-[2-Chloro-4-({7-methoxy-6-[2-(4-methylpiperazino)ethoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea

N-{2-Chloro-4-[(6-hydroxy-7-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (500 mg), potassium carbonate (857 mg), and 1,3-dibromopropane (0.5 ml) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform/2-propanol (4/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 451 mg (yield 71%) of N-(4-{[6-(2-bromoethoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea. N-(4-{[6-(2-Bromoethoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea (50 mg), potassium carbonate (40 mg), and N-methylpiperazine (50 µl) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 20 mg (yield 44%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, J = 7.3 Hz, 3H), 1.56 - 1.65 (m, 2H), 1.77 (br, 4H), 2.31 (s, 3H), 2.53 (br, 2H), 2.71 (br, 2H), 2.97 (t, J = 6.1 Hz, 3H), 3.24 - 3.29 (m, 2H), 4.04 (s, 3H), 4.32 (t, J = 6.1 Hz, 2H),

4.83 (br, 1H), 6.69 (s, 1H), 7.16 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.30 (s, 1H), 7.31 (s, 1H), 7.55 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.62 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 529 (M^++1)

Example 137: N-[2-Chloro-4-({7-methoxy-6-[3-(4-methylpiperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-propylurea

N-{2-Chloro-4-[(6-hydroxy-7-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea (500 mg), potassium carbonate (857 mg), and 1,3-dibromopropane (0.5 ml) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform/2-propanol (4/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 451 mg (yield 71%) of N-(4-{[6-(3-bromopropoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea. N-(4-{[6-(3-Bromopropoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea (50 mg), potassium carbonate (40 mg), and N-methylpiperazine (50 µl) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 20 mg (yield 44%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, J = 7.6 Hz, 3H), 1.58 - 1.64 (m, 2H), 1.71 (br, 4H), 2.31 (s, 3H), 2.53 (br, 2H), 2.71 (br, 2H), 2.11 - 2.17 (m, 2H), 2.30 (s,

3H), 2.59 - 2.62 (m, 2H), 3.24 - 3.29 (m, 2H), 4.04 (s, 3H), 4.26 (t, J = 6.6 Hz, 2H), 4.80 (br, 1H), 6.67 (s, 1H), 7.17 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.31 (s, 1H), 7.31 (s, 1H), 7.52 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.61 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 543 (M^++1)

Example 138: N-(2-Chloro-4-{[7-methoxy-6-(2-pyridylmethoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(6-hydroxy-7-methoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 2-(chloromethyl)pyridine hydrochloride (41 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 120°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ethyl acetate to give 54 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.51 - 1.58 (m, 2H), 3.17 - 3.22 (m, 2H), 4.02 (s, 3H), 4.69 (br, 1H), 5.36 (s, 2H), 6.57 (s, 1H), 7.08 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.21 - 7.29 (m, 2H), 7.53 - 7.55 (m, 2H), 7.66 - 7.71 (m, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.55 - 8.57 (m, 2H)

Mass analysis, found (ESI-MS, m/z): 494 (M^++1)

Example 139: N-(2-Chloro-4-{[7-methoxy-6-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

A starting compound (N-(4-{[6-(3-propoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propylurea, 54 mg), potassium carbonate (138 mg), and morpholine (0.017 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 120°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over

anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ethyl acetate to give 42 mg (yield 77%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.47 - 1.59 (m, 4H), 1.88 - 2.00 (m, 2H), 2.35 - 2.48 (m, 4H), 3.20 (dd, J = 7.3 Hz, 12.9 Hz, 2H), 3.62 - 3.74 (m, 4H), 3.97 (s, 3H), 4.15 (t, J = 6.3 Hz, 2H), 4.74 - 4.80 (m, 1H), 6.63 (s, 1H), 7.09 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 7.42 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.54 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 530 (M^++1)

Example 140: N-{2-Chloro-4-[(6-{3-(2-hydroxyethyl)-(methyl)amino]propoxy}-7-methoxy-4-quinazolinyl)oxy]-phenyl}-N'-propylurea

A starting compound (N-(4-{[6-(3-bromopropoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-propylurea, 51 mg), potassium carbonate (68 mg), and 2-(methylamino)ethanol (15 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 25 mg (yield 48%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, J = 7.6 Hz, 3H), 1.53 - 1.62 (m, 2H), 2.08 - 2.15 (m, 2H), 2.30 (s, 3H), 2.58 (t, J = 5.4 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 3.21 - 3.26 (m, 2H), 3.60 (t, J = 5.4 Hz, 2H), 4.02 (s, 3H), 4.23 (t, J = 6.3 Hz, 2H), 5.06 (t, J = 5.6 Hz, 1 Hz), 6.79 (s, 1H), 7.13 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.27 - 7.28 (m, 2H), 7.48 (s, 1H), 8.21 (d, J = 9.0 Hz, 1H), 8.58 (s, 1H)

Example 141: N-(2-Chloro-4-{[6-methoxy-7-(2-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 2-chloromethylpyridine hydrochloride (41 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 81 mg (yield 82%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.54 - 1.65 (m, 2H), 3.25 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 4.05 (s, 3H), 4.75 - 4.82 (m, 1H), 5.42 (s, 2H), 6.46 (d, J = 5.4 Hz, 1H), 6.67 (s, 1H), 7.08 (dd, J = 2.9 Hz, 9.0 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.44 (s, 1H), 7.53 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.69 (dt, J = 2.0 Hz, 7.8 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 5.1 Hz, 1H), 8.61 (d, J = 4.6 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 493 (M^++1)

Example 142: N-(2-Chloro-4-{[6-methoxy-7-(3-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 3-chloromethylpyridine hydrochloride (41 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 70 mg (yield 71%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.3 Hz, 3H), 1.54 - 1.65 (m, 2H), 3.25 (dd, J = 7.3 Hz, 12.9 Hz, 2H),

4.02 (s, 3H), 4.82 - 4.90 (m, 1H), 5.30 (s, 2H), 6.47 (d, J = 5.4 Hz, 1H), 6.72 (s, 1H), 7.09 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.32 (dd, J = 4.9 Hz, 7.8 Hz, 1H), 7.47 (s, 1H), 7.52 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 9.3 Hz, 1H), 8.47 (d, J = 5.4 Hz, 1H), 8.58 (d, J = 3.2 Hz, 1H), 8.75 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 493 (M^++1)

Example 143: N-(2-Chloro-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 4-chloromethylpyridine hydrochloride (41 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC to give 71 mg (yield 71%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.54 - 1.65 (m, 2H), 3.25 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 4.05 (s, 3H), 4.86 - 4.92 (m, 1H), 5.32 (s, 2H), 6.48 (d, J = 4.7 Hz, 1H), 6.73 (s, 1H), 7.08 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.19 (d, J = 2.9 Hz, 1H), 7.38 (s, 1H), 7.41 (d, J = 6.1 Hz, 2H), 7.54 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 5.4 Hz, 1H), 8.61 (d, J = 6.1 Hz, 2H)

Mass analysis, found (ESI-MS, m/z): 493 (M^++1)

Example 144: N-(2-Chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 100 mg), potassium carbonate (172 mg), and 1,2-dibromoethane (0.086 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 3 hr. Water was added to the reaction mixture, and

the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea). The intermediate, potassium carbonate (138 mg), and morpholine (0.17 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 70 mg (yield 54%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.50 - 1.59 (m, 2H), 2.57 (t, J = 4.6 Hz, 4H), 2.88 (t, J = 5.9 Hz, 2H), 3.18 - 3.23 (m, 2H), 3.68 (t, J = 4.6 Hz, 4H), 3.94 (s, 3H), 4.26 (t, J = 5.9 Hz, 2H), 4.98 (t, J = 5.3 Hz, 2H), 6.41 (d, J = 5.3 Hz, 1H), 6.74 (br, 1H), 7.03 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.34 (s, 1H), 7.43 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 515 (M^++1)

Example 145: N-[2-Chloro-4-({6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 2-(1H-1,2,3-triazol-1-yl)ethyl 4-methyl-1-benzenesulfonate (59 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 120°C for 5 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was

dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform-methanol to give 92 mg (yield 92%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.57 - 1.63 (m, 2H), 3.23 - 3.28 (m, 2H), 4.01 (s, 3H), 4.52 (t, J = 5.1 Hz, 2H), 4.81 (br, 1H), 4.93 (t, J = 5.1 Hz, 2H), 6.47 (d, J = 5.4 Hz, 1H), 6.69 (s, 1H), 7.08 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 7.51 (s, 1H), 7.72 (d, J = 1.0 Hz, 1H), 7.97 (d, J = 1.0 Hz, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 497 (M^++1)

Example 146: N-[2-Chloro-4-({7-[2-(1H-1-imidazolyl)-ethoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 2-(1H-1-imidazolyl)ethyl 4-methyl-1-benzenesulfonate (59 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 120°C for 5 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by HPLC by development with chloroform/methanol to give 81 mg (yield 82%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J = 7.6 Hz, 3H), 1.50 - 1.65 (m, 2H), 1.90 - 2.08 (m, 2H), 3.24 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 4.01 (s, 3H), 4.17 (t, J = 6.6 Hz, 2H), 4.44 (t, J = 7.3 Hz, 2H), 4.88 - 4.94 (m, 1H), 6.32 (s, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.25 (s, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.48 (s, 1H), 7.55 (s, 1H), 7.70 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.58 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 496 (M^++1)

Example 147: N-(2-Chloro-4-{[7-(3-hydroxypropoxy)-6-methoxy-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 3-bromo-1-propanol (0.027 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 94 mg (yield 100%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.6 Hz, 3H), 1.45 - 1.62 (m, 2H), 2.09 - 2.18 (m, 2H), 3.21 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 3.87 (t, J = 5.6 Hz, 2H), 3.94 (s, 3H), 4.31 (t, J = 6.1 Hz, 2H), 4.81 - 4.87 (m, 1H), 6.42 (d, J = 5.1 Hz, 1H), 6.69 (s, 1H), 7.03 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.36 (s, 1H), 7.43 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H)

Example 148: N-[2-Chloro-4-({6-methoxy-7-[2-(4-methylpiperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea

A starting compound (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea, 50 mg), potassium carbonate (138 mg), and 1-methylpiperazine (0.055 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 54 mg (yield 100%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.3 Hz, 3H),

1.49 - 1.62 (m, 2H), 2.24 (s, 3H), 2.35 - 2.70 (m, 2H), 2.90 (t, J = 4.6 Hz, 2H), 3.21 (dd, J = 7.3 Hz, 12.9 Hz, 2H), 3.94 (s, 3H), 4.26 (t, J = 6.1 Hz, 2H), 4.75 - 4.85 (m, 1H), 6.41 (d, J = 5.1 Hz, 1H), 6.67 (s, 1H), 7.04 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.34 (s, 1H), 7.42 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 528 (M^++1)

Example 149: N-(2-Chloro-4-{[7-(2-hydroxyethoxy)-6-methoxy-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 2-bromoethanol (0.021 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 80 mg (yield 90%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J = 7.6 Hz, 3H), 1.54 - 1.65 (m, 2H), 3.25 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 3.99 (s, 3H), 4.07 (t, J = 4.4 Hz, 2H), 4.28 (t, J = 4.6 Hz, 2H), 6.46 (d, J = 5.4 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 7.08 (s, 1H), 7.08 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.42 (s, 1H), 7.49 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 2.9 Hz, 1H)

Example 150: N-{2-Chloro-4-[(7-{2-[(2-hydroxyethyl)-(methyl)amino]ethoxy}-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea

A starting compound (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea, 50 mg), potassium carbonate (138 mg), and 2-(methylamino)ethanol (0.040 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred

at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 53 mg (yield 106%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.54 - 1.65 (m, 2H), 2.42 (s, 3H), 2.69 (t, J = 5.1 Hz, 2H), 3.00 (t, J = 5.6 Hz, 2H), 3.26 (dd, J = 7.1 Hz, 12.7 Hz, 2H), 3.64 (t, J = 5.1 Hz, 2H), 3.99 (s, 3H), 4.26 (t, J = 5.6 Hz, 2H), 4.66 - 4.69 (m, 1H), 6.46 (d, J = 5.1 Hz, 1H), 6.70 (s, 1H), 7.09 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.39 (s, 1H), 7.47 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 503 (M^++1)

Example 151: N-(2-Chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea, 52 mg), potassium carbonate (138 mg), and morpholine (0.044 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 23 mg (yield 44%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.6 Hz, 3H), 1.49 - 1.60 (m, 2H), 2.02 - 2.11 (m, 2H), 2.40 - 2.47 (m, 4H), 2.52 (t, J = 7.1 Hz, 2H), 3.21 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 3.62 - 3.69 (m, 4H), 3.95 (s, 3H), 4.20 (t, J = 6.6 Hz, 2H), 4.70 - 4.78 (m, 1H), 6.41 (d, J = 5.1 Hz, 1H), 6.64 (s, 1H), 7.04 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 7.43 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H)

Example 152: N-[2-Chloro-4-(6-methoxy-7-{[3-(4-methylpiperazino)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea, 52 mg), potassium carbonate (138 mg), and 1-methylpiperazine (0.055 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 41 mg (yield 76%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.6 Hz, 3H), 1.49 - 1.64 (m, 2H), 2.02 - 2.10 (m, 2H), 2.23 (s, 3H), 2.30 - 2.56 (m, 8H), 2.52 (t, J = 7.3 Hz, 2H), 3.20 (dd, J = 7.1 Hz, 12.9 Hz, 2H), 3.94 (s, 3H), 4.19 (t, J = 6.8 Hz, 2H), 4.83 - 4.92 (m, 1H), 6.40 (d, J = 5.1 Hz, 1H), 6.69 (s, 1H), 7.03 (dd, J = 2.9 Hz, 9.3 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.35 (s, 1H), 7.42 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H)

Mass analysis, found (*ESI-MS*, m/z): 542 (M^++1)

Example 153: N-[2-Chloro-4-(6-methoxy-7-{[3-(1*H*-1,2,3-triazol-1-yl)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea

Triazole (0.41 ml), 1-bromo-3-chloropropane (0.79 ml), tetrabutylammonium iodide (10 mg), and a 3 M aqueous sodium hydroxide solution (1 ml) were dissolved in acetone (10 ml), and the solution was stirred at 50°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography by development with chloroform to give an intermeidate (327 mg).

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and the intermediate (43 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 54 mg (yield 52%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.54 - 1.65 (m, 2H), 2.49 - 2.58 (m, 2H), 3.26 (dd, J = 7.1 Hz, 13.2 Hz, 2H), 4.01 (s, 3H), 4.15 (t, J = 5.9 Hz, 2H), 4.69 (t, J = 6.6 Hz, 2H), 4.90 - 5.00 (m, 1H), 6.46 (d, J = 5.1 Hz, 1H), 6.77 (s, 1H), 7.08 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.36 (s, 1H), 7.51 (s, 1H), 7.61 (s, 1H), 7.67 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.47 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 511 (M^++1)

Example 154: N-[2-Chloro-4-({7-[3-(1H-1-imidazolyl)-propoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea

Imidazole (680 mg), 1-bromo-3-chloropropane (0.79 ml), tetrabutylammonium iodide (10 mg), and a 3 M aqueous sodium hydroxide solution (1 ml) were dissolved in acetone (10 ml), and the solution was stirred at 50°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography by development with chloroform to give an intermediate (1-(3-chloropropyl)-1H-imidazole, 525 mg).

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and the intermediate (42

mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 23 mg (yield 23%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.48 - 1.60 (m, 2H), 2.27 - 2.36 (m, 2H), 3.20 (dd, J = 6.8 Hz, 12.9 Hz, 2H), 3.97 (s, 3H), 4.06 (t, J = 5.9 Hz, 2H), 4.21 (t, J = 6.8 Hz, 2H), 6.39 (d, J = 5.4 Hz, 1H), 6.90 (s, 1H), 6.98 - 7.04 (m, 2H), 7.12 (d, J = 2.7 Hz, 1H), 7.30 (s, 1H), 7.44 - 7.48 (m, 2H), 8.22 (d, J = 9.0 Hz, 1H), 8.41 (d, J = 5.4 Hz, 1H)

Example 155: N-{2-Chloro-4-[(7-{2-[di(2-hydroxyethyl)-amino]ethoxy}-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea

A starting compound (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea, 50 mg), potassium carbonate (138 mg), and 1-methylpiperazine (0.055 ml) were dissolved in N,N-dimethylformamide (1 ml), and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 46 mg (yield 92%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.3 Hz, 3H), 1.50 - 1.60 (m, 2H), 2.74 (t, J = 4.9 Hz, 4H), 3.04 (t, J = 4.9 Hz, 2H), 3.15 - 3.24 (m, 2H), 3.60 (t, J = 5.1 Hz, 4H), 3.94 (s, 3H), 4.17 (t, J = 5.0 Hz, 2H), 6.41 (d, J = 5.4 Hz, 1H), 6.75 (s, 1H), 7.04 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.38 (s, 1H), 7.43 (s,

1H), 8.19 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H)

Example 156: N-{2-Chloro-4-[(7-{3-[di(2-hydroxyethyl)-amino]propoxy}-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea, 52 mg), potassium carbonate (138 mg), and diethanolamine (53 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 41 mg (yield 82%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J = 7.3 Hz, 3H), 1.46 - 1.56 (m, 2H), 1.97 - 2.05 (m, 2H), 2.63 (t, J = 5.1 Hz, 4H), 2.69 (t, J = 6.1 Hz, 2H), 3.19 (dd, J = 7.1 Hz, 13.2 Hz, 2H), 3.60 (t, J = 4.9 Hz, 4H), 3.94 (s, 3H), 4.32 (t, J = 5.9 Hz, 2H), 5.27 - 5.35 (m, 1H), 6.37 (d, J = 5.4 Hz, 1H), 6.94 (s, 1H), 7.01 (dd, J = 2.9 Hz, 9.0 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H), 7.42 (s, 1H), 7.53 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.35 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 547 (M^++1)

Example 157: N-{2-Chloro-4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-propylurea, 52 mg), potassium carbonate (138 mg), and 2-(methylamino)ethanol (0.040 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The

residue was washed with ether to give 51 mg (yield 98%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.45 - 1.59 (m, 2H), 2.05 (t, J = 6.8 Hz, 2H), 2.24 (s, 3H), 2.51 (t, J = 5.1 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 3.20 (dd, J = 6.8 Hz, 12.9 Hz, 2H), 3.57 (t, J = 5.4 Hz, 2H), 3.95 (s, 3H), 4.22 (t, J = 6.3 Hz, 2H), 5.00 - 5.08 (m, 1H), 6.40 (d, J = 5.1 Hz, 1H), 6.79 (s, 1H), 7.03 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.13 (d, J = 2.7 Hz, 1H), 7.426 (s, 1H), 7.433 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.40 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 517 (M^++1)

Example 158: N-[2-Chloro-4-({6-methoxy-7-[4-(1*H*-1,2,3-triazol-1-yl)butoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea

Triazole (0.41 ml), 1-bromo-4-chlorobutane (0.93 ml), tetrabutylammonium iodide (10 mg), and a 3 M aqueous sodium hydroxide solution (1 ml) were dissolved in acetone (10 ml), and the solution was stirred at 50°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography by development with chloroform to give an intermediate (1-(4-chlorobutyl)-1H-1,2,3-triazole, 314 mg).

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and the intermediate (48 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 42 mg

(yield 40%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J = 7.3 Hz, 3H), 1.54 - 1.65 (m, 2H), 1.88 - 1.98 (m, 2H), 2.14 - 2.24 (m, 2H), 3.26 (dd, J = 6.6 Hz, 13.2 Hz, 2H), 3.99 (s, 3H), 4.20 (t, J = 5.9 Hz, 2H), 4.55 (t, J = 7.1 Hz, 2H), 5.00 - 5.06 (m, 1H), 6.46 (d, J = 5.4 Hz, 1H), 6.80 (s, 1H), 7.08 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 7.49 (s, 1H), 7.68 - 7.72 (m, 2H), 8.26 (d, J = 9.0 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 525 (M^++1)

Example 159: N-{2-Chloro-4-[(6-methoxy-7-{[5-(1*H*-1,2,3-triazol-1-yl)pentyl]oxy}-4-quinolyl)oxy]phenyl}-N'-propylurea

Triazole (0.41 ml), 1-bromo-5-chloropentane (1.0 ml), tetrabutylammonium iodide (10 mg), and a 3 M aqueous sodium hydroxide solution (1 ml) were dissolved in acetone (10 ml), and the solution was stirred at 50°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography by development with chloroform to give an intermediate (1-(5-chloropentyl-1H-1,2,3-triazole, 390 mg).

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and the intermediate (51 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 33 mg (yield 31%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.6 Hz, 3H),

1.47 - 1.59 (m, 2H), 1.85 - 2.03 (m, 4H), 3.21 (dd, J = 6.6 Hz, 13.2 Hz, 2H), 3.94 (s, 3H), 4.11 (t, J = 6.3 Hz, 2H), 4.38 (t, J = 7.1 Hz, 2H), 4.86 - 4.94 (m, 1H), 6.41 (d, J = 5.4 Hz, 1H), 6.71 (s, 1H), 7.03 (dd, J = 2.4 Hz, 9.0 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.31 (s, 1H), 7.43 (s, 1H), 7.51 (s, 1H), 7.64 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.41 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 539 (M^++1)

Example 160: N-[2-Chloro-4-({7-[4-(1*H*-1-imidazolyl)-butoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea

Imidazole (680 mg), 1-bromo-4-chlorobutane (0.93 ml), tetrabutylammonium iodide (10 mg), and a 3 M aqueous sodium hydroxide solution (1 ml) were dissolved in acetone (10 ml), and the solution was stirred at 50°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography by development with chloroform to give an intermediate (1-(4-chlorobutyl)-1H-imidazole, 756 mg).

A starting compound (N-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and the intermediate (48 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 29 mg (yield 28%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J = 7.3 Hz, 3H), 1.54 - 1.65 (m, 2H), 1.83 - 1.95 (m, 2H), 1.98 - 2.08 (m, 2H), 3.25 (dd, J = 6.8 Hz, 12.7 Hz, 2H), 4.00 (s, 3H), 4.10 (t, J = 7.1 Hz, 2H), 4.20 (t, J = 6.1 Hz, 2H), 5.08

- 5.16 (m, 1H), 6.46 (d, J = 5.1 Hz, 1H), 6.83 (s, 1H), 6.97 (s, 1H), 7.06 (s, 1H), 7.08 (dd, J = 2.9 Hz, 9.3 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 7.49 (s, 1H), 7.58 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Example 161: N-(2-Chloro-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluorophenyl)urea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-(2,4-difluorophenyl)urea, 80 mg), potassium carbonate (138 mg), and 4-chloromethylpyridine hydrochloride (41 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 50 mg (yield 52%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.03 (s, 3H), 5.46 (s, 2H), 7.03 - 7.11 (m, 1H), 7.28 - 7.38 (m, 1H), 7.47 (s, 1H), 7.50 (d, J = 5.9 Hz, 2H), 7.56 (d, J = 2.7 Hz, 1H), 7.61 (s, 1H), 7.95 (s, 1H), 8.09 - 8.18 (m, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.57 (s, 1H), 8.63 (d, J = 5.9 Hz, 2H), 8.81 (s, 1H), 9.30 (s, 1H)

Example 162: N-(2-Chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluorophenyl)urea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-(2,4-difluorophenyl)urea, 100 mg), potassium carbonate (857 mg), and 1,2-dibromoethane (0.085 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried

over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea). The intermediate, potassium carbonate (138 mg), and morpholine (0.05 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 57 mg (yield 46%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.54 - 2.63 (m, 4H), 2.85 - 2.94 (m, 2H), 3.66 - 3.73 (m, 4H), 3.97 (s, 3H), 4.25 - 4.32 (m, 2H), 6.77 - 6.88 (m, 2H), 7.09 (s, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.257 (s, 1H), 7.264 (s, 1H), 7.44 (s, 1H), 7.90 - 7.99 (m, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.56 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 586 (M^++1)

Example 163: N-(2-Chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluorophenyl)urea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea, 59 mg), potassium carbonate (857 mg), and morpholine (0.043 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 53 mg (yield 89%)

of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.06 - 2.16 (m, 2H), 2.43 - 2.57 (m, 4H), 2.56 (t, J = 6.8 Hz, 2H), 3.68 - 3.75 (m, 4H), 4.03 (s, 3H), 4.27 (t, J = 6.6 Hz, 2H), 6.79 - 6.91 (m, 2H), 7.14 (s, 1H), 7.19 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.28 (s, 1H), 7.29 (d, J = 9.0 Hz, 1H), 7.33 (s, 1H), 7.49 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.61 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 600 (M^++1)

Example 164: N-[2-Chloro-4-({6-methoxy-7-[3-(4-methyl-piperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea, 59 mg), potassium carbonate (138 mg), and 1-methylpiperazine (0.055 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 58 mg (yield 95%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.01 - 2.12 (m, 2H), 2.23 (s, 3H), 2.23 - 2.80 (m, 8H), 2.51 (t, J = 7.1 Hz, 2H), 3.97 (s, 3H), 4.20 (t, J = 7.2 Hz, 2H), 6.73 - 6.87 (m, 2H), 7.13 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 7.27 (s, 1H), 7.30 (s, 1H), 7.44 (s, 1H), 7.91 - 8.00 (m, 2H), 8.21 (d, J = 9.0 Hz, 1H), 8.56 (s, 1H)

Example 165: N-{2-Chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinazolinyl)oxy]-phenyl}-N'-(2,4-difluorophenyl)urea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea, 59 mg), potassium carbonate (138 mg), and 2-(methylamino)ethanol (0.040 ml) were dissolved in N,N-dimethylformamide (1 ml), and the

solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 58 mg (yield 100%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.06 - 2.16 (m, 2H), 2.30 (s, 3H), 2.57 (t, J = 5.1 Hz, 2H), 2.65 (t, J = 6.8 Hz, 1H), 3.63 (t, J = 5.4 Hz, 2H), 4.02 (s, 3H), 4.28 (t, J = 6.1 Hz, 2H), 6.79 - 6.91 (m, 2H), 7.18 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 7.48 (s, 1H), 7.96 - 8.06 (m, 2H), 8.26 (d, J = 9.0 Hz, 1H), 8.59 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 588 (M^++1)

Example 166: N-[2-Chloro-4-({6-methoxy-7-[2-(4-methylpiperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea

A starting compound (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea, 50 mg), potassium carbonate (138 mg), and 1-methylpiperazine (0.055 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 48 mg (yield 93%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.31 (s, 3H), 2.40 - 2.75 (m, 8H), 2.95 (t, J = 6.1 Hz, 2H), 3.99 (s, 3H), 4.31 (t, J = 5.9 Hz, 2H), 6.48 (d, J = 5.1 Hz, 1H), 6.85 - 6.96 (m, 3H), 7.12 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.15 (s, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.40 (s, 1H), 7.47 (s, 1H), 7.94 - 8.03 (m, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 5.1 Hz, 1H)

Example 167: N-{2-Chloro-4-[(7-{2-[(2-hydroxyethyl)-(methyl)amino]ethoxy}-6-methoxy-4-quinolyl)oxy]phenyl}-N'-(2,4-difluorophenyl)urea

A starting compound (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea, 50 mg), potassium carbonate (138 mg), and 2-(methylamino)ethanol (0.040 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 48 mg (yield 97%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H), 2.71 (t, J = 4.9 Hz, 2H), 3.02 (t, J = 5.6 Hz, 4H), 3.66 (t, J = 5.1 Hz, 2H), 3.97 (s, 3H), 4.27 (t, J = 5.6 Hz, 2H), 6.46 (d, J = 5.4 Hz, 1H), 6.80 - 6.93 (m, 2H), 7.11 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.45 (s, 1H), 7.96 - 8.04 (m, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Example 168: N-(2-Chloro-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)urea

A starting compound (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-(2,4-difluorophenyl)urea, 50 mg), potassium carbonate (138 mg), and morpholine (0.044 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 32 mg (yield 64%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.06 - 2.16 (m, 2H), 2.43 - 2.51 (m, 4H), 2.56 (t, J = 7.3 Hz, 2H), 3.68 - 3.74 (m, 4H), 4.00 (s, 3H), 4.25 (t, J = 6.6 Hz, 2H), 6.47 (d, J = 5.1 Hz, 1H), 6.84 - 6.93 (m, 2H), 7.06 (s, 1H), 7.12 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.22 (d, J = 2.9 Hz, 1H), 7.42 (s, 1H), 7.47 (s, 1H), 7.95 - 8.04 (m, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Example 169: N-(2-Chloro-4-{[6-methoxy-7-(3-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)urea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-(2,4-difluorophenyl)urea (55 mg), potassium carbonate (31 mg), and 3-picolyl chloride hydrochloride (22 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for one hr. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 30 mg (yield 48%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.03 (s, 3H), 5.31 (s, 2H), 6.49 (d, J = 5.4 Hz, 1H), 6.77 - 6.88 (m, 2H), 7.10 - 7.16 (m, 2H), 7.31 - 7.35 (m, 1H), 7.48 (s, 1H), 7.54 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H), 8.03 - 8.10 (m, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.42 (s, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.59 (d, J = 3.9 Hz, 1H), 8.77 (s, 1H)

Example 170: N-[2-Chloro-4-({6-methoxy-7-[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-(2,4-difluorophenyl)urea (55 mg), potassium carbonate (31 mg), and 2-(1H-1,2,3-triazol-1-

yl)ethyl 4-methyl-1-benzenesulfonate (36 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for one hr. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 46 mg (yield 72%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.02 (s, 3H), 4.53 (d, J = 4.9 Hz, 2H), 4.95 (d, J = 5.1 Hz, 2H), 6.47 (d, J = 5.1 Hz, 1H), 6.83 - 6.92 (m, 2H), 7.11 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.16 (d, J = 2.7 Hz, 1H), 7.39 (s, 1H), 7.52 (s, 1H), 7.58 (s, 1H), 7.70 (s, 1H), 7.76 (s, 1H), 8.00 (s, 1H), 8.01 - 8.07 (m, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H)

Example 171: N-(2-Methoxy-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea

N-4-[(7-Hydroxy-6-methoxy-4-quinazolinyl)oxy]-2-methoxyphenyl}-N'-propylurea (100 mg), potassium carbonate (138 mg), and 1,3-dibromopropane (56 mg) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform/2-propanol (4/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 53 mg (yield 41%) of N-(4-[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy-2-methoxyphenyl}-N'-propylurea. N-(4-{[6-(3-Bromopropoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea (50 mg), potassium carbonate (60 mg), and N-methylpiperazine (100 µl) were dissolved in N,N-

dimethylformamide (2 ml), and the solution was stirred at room temperature for 16 hr. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 22 mg (yield 42%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.56 - 1.60 (m, 2H), 2.14 (br, 2H), 2.50 (br, 4H), 2.58 (br, 2H), 3.23 - 3.26 (m, 2H), 3.74 (br, 4H), 3.87 (s, 3H), 4.04 (s, 3H), 4.27 - 4.31 (m, 2H), 4.62 - 4.64 (m, 1H), 6.65 (s, 1H), 6.79 - 6.85 (m, 2H), 7.33 (s, 1H), 7.53 (s, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.62 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 526 (M^++1)

Example 172: N-(2,4-Difluorophenyl)-N'-{2-methoxy-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinazolinyl]oxy}-phenyl}urea

N-(2,4-Difluorophenyl)-N'-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]-2-methoxyphenylurea (375 mg), potassium carbonate (442 mg), and 1,3-dibromopropane (242 mg) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 3 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 210 mg (yield 45%) of N-{4-[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy-2-methoxyphenyl}-N'-(2,4-difluoro-phenyl)urea. N-(4-{[6-(3-Bromopropoxy)-7-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl}-N'-propylurea (130 mg), triethylamine (0.5 ml), and morpholine (0.5 ml) were

dissolved in N,N-dimethylformamide (4 ml), and the solution was stirred at room temperature for 18 hr. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 81 mg (yield 62%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.97 - 2.00 (m, 2H), 2.39 (br, 4H), 2.49 - 2.51 (m, 2H), 3.58 - 3.60 (m, 4H), 3.88 (s, 3H), 3.98 (s, 3H), 4.25 (t, J = 6.3 Hz, 2H), 4.27 - 4.31 (m, 2H), 4.62 - 4.64 (m, 1H), 6.84 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 7.03 - 7.07 (m, 2H), 7.28 - 7.34 (m, 1H), 7.38 (s, 1H), 7.55 (s, 1H), 8.11 - 8.17 (m, 2H), 8.55 (s, 1H), 8.74 (s, 1H), 9.18 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 596 (M^++1)

Example 173: N-(2-Methoxy-4-{[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]-2-methoxyphenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 1,3-dibromopropane(0.10 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate. The intermediate, potassium carbonate (138 mg), and morpholine (0.040 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with

chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol to give 74 mg (yield 71%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, J = 7.6 Hz, 3H), 1.52 - 1.69 (m, 2H), 2.06 - 2.15 (m, 2H), 2.43 - 2.49 (m, 4H), 2.55 (t, J = 7.3 Hz, 2H), 3.23 (dd, J = 6.1 Hz, 12.9 Hz, 2H), 3.67 - 3.72 (m, 4H), 3.81 (s, 3H), 4.00 (s, 3H), 4.24 (t, J = 6.8 Hz, 2H), 6.44 (d, J = 5.1 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.40 (s, 1H), 7.53 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H)

Example 174: N-(2-Methoxy-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea

A starting compound (N-{4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]-2-methoxyphenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 4-chloromethylpyridine hydrochloride (48 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 65 mg (yield 67%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, J = 7.3 Hz, 3H), 1.52 - 1.69 (m, 2H), 3.24 (dd, J = 7.3 Hz, 12.9 Hz, 2H), 3.82 (s, 3H), 4.06 (s, 3H), 4.63 - 4.69 (m, 1H), 5.32 (s, 2H), 6.46 (d, J = 5.4 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.77 (dd, J = 2.4 Hz, 8.5 Hz, 1H), 7.37 (s, 1H), 7.42 (d, J = 6.1 Hz, 2H), 7.59 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.43 (d, J = 5.4 Hz, 1H), 8.61 (d, J = 6.1 Hz, 2H)

Example 175: N-Ethyl-N'-(4-{[6-methoxy-7-(2-morpholino-

ethoxy)-4-quinolyl]oxy}-2,5-dimethylphenyl)urea

A starting compound (N-ethyl-N'-{4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}urea, 76 mg), potassium carbonate (138 mg), and 1,2-dibromoethane (0.085 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate (N-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-ethylurea). The intermediate, potassium carbonate (138 mg), and morpholine (0.044 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 72 mg (yield 73%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.10 (t, J = 7.3 Hz, 3H), 2.07 (s, 3H), 2.16 (s, 3H), 2.53 - 2.59 (m, 4H), 2.88 (t, J = 5.9 Hz, 2H), 3.20 - 3.30 (m, 2H), 3.66 - 3.71 (m, 4H), 3.96 (s, 3H), 4.26 (t, J = 5.9 Hz, 2H), 4.73 - 4.82 (m, 1H), 6.16 (s, 1H), 6.23 (d, J = 5.4 Hz, 1H), 6.88 (s, 1H), 7.35 (s, 1H), 7.40 (s, 1H), 7.50 (s, 1H), 8.38 (d, J = 5.1 Hz, 1H)

Example 176: N-[4-({6-Methoxy-7-[3-(4-methylpiperazino)-propoxy]-4-quinolyl}oxy)-2,5-dimethylphenyl]-N'-propylurea

A starting compound (N-{4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}-N'-propylurea, 80 mg), potassium carbonate (138 mg), and 1,3-

dibromopropane(0.10 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate (N-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-propylurea). The intermediate, potassium carbonate (138 mg), and 1-methylpiperazine (0.055 ml) were dissolved in N,N-dimethylformamide (1 ml), and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 33 mg (yield 31%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.50 - 1.58 (m, 2H), 2.07 - 2.20 (m, 2H), 2.12 (s, 3H), 2.23 (s, 3H), 2.28 (s, 3H), 2.33 - 2.70 (m, 10H), 3.21 (dd, J = 7.3 Hz, 13.4 Hz, 2H), 4.00 (s, 3H), 4.24 (t, J = 6.6 Hz, 2H), 4.64 - 4.76 (m, 1H), 5.95 - 6.05 (m, 1H), 6.27 (d, J = 5.1 Hz, 1H), 6.95 (s, 1H), 7.39 - 7.43 (m, 2H), 7.54 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 536 (M^++1)

Example 177: N-(2,4-Difluorophenyl)-N'-[4-({6-methoxy-7-[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)-2,5-dimethylphenyl]urea

A starting compound (N-(2,4-difluorophenyl)-N'-{4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]-2,5-dimethylphenyl}urea, 93 mg), potassium carbonate (138 mg), and 2-(1H-1,2,3-triazol-1-yl)ethyl 4-methyl-1-benzenesulfonate (52 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for 5 hr. Water was added to the reaction

mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 33 mg (yield 30%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.10 (s, 3H), 2.19 (s, 3H), 4.01 (s, 3H), 4.51 (t, J = 4.9 Hz, 2H), 4.93 (t, J = 5.4 Hz, 2H), 4.94 (s, 1H), 6.28 (d, J = 5.1 Hz, 1H), 6.75 - 6.88 (m, 2H), 6.90 (s, 1H), 7.36 (s, 1H), 7.58 (s, 1H), 7.60 (s, 1H), 7.73 (s, 1H), 7.99 (s, 1H), 8.08 (dd, J = 9.3 Hz, 15.1 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H)

Example 178: N'-(2-Chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinazolinyl]oxy}phenyl)-N,N-dimethylurea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-dimethylurea, 80 mg), potassium carbonate (138 mg), and 1,2-dibromoethane (0.085 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate (N'-(4-{[7-(2-bromoethoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N,N-dimethylurea). The intermediate, potassium carbonate (138 mg), and morpholine (0.043 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 72 mg (yield 72%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.58 - 2.66 (m, 4H), 2.90 - 2.98 (m, 2H), 3.08 (s, 6H), 3.70 - 3.79 (m, 4H), 4.02 (s, 3H), 4.29 - 4.37 (m, 2H), 6.97 (s, 1H), 7.15 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.24 - 7.26 (m, 1H), 7.29 (s, 1H), 7.49 (s, 1H), 8.36 (d, J = 9.3 Hz, 1H), 8.60 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 502 (M^++1)

Example 179: N'-(2-Chloro-4-{[6-methoxy-7-(4-morpholinobutoxy)-4-quinazolinyl]oxy}phenyl)-N,N-dimethylurea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-dimethylurea, 80 mg), potassium carbonate (138 mg), and 1,4-dibromobutane (0.12 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give an intermediate (N'-(4-{[7-(4-bromobutoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N,N-dimethylurea). The intermediate, potassium carbonate (138 mg), and morpholine (0.043 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 47 mg (yield 44%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.67 - 1.77 (m, 2H), 1.93 - 2.03 (m, 2H), 2.39 - 2.50 (m, 4H), 3.67 (s, 6H), 3.64 - 3.75 (m, 4H), 4.02 (s, 3H), 4.21 (t, J = 6.6 Hz, 2H), 6.97 (s, 1H), 7.16 (dd, J = 2.7 Hz, 9.3 Hz, 1H), 7.26 (s, 1H), 7.28 (s, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.48 (s, 1H), 8.36 (d, J = 9.3 Hz, 1H), 8.59 (s, 1H)

Example 180: N'-(2-Chloro-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinazolinyl]oxy}phenyl)-N,N-dimethylurea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-dimethylurea, 50 mg), potassium carbonate (138 mg), and 4-chloromethylpyridine hydrochloride (49 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 37 mg (yield 60%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.07 (s, 6H), 4.07 (s, 3H), 5.32 (s, 2H), 6.97 (s, 1H), 7.15 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.26 (s, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.41 (d, J = 6.1 Hz, 1H), 7.55 (s, 1H), 8.37 (d, J = 9.0 Hz, 1H), 8.58 (s, 1H), 8.63 (d, J = 6.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 480 (M^++1)

Example 181: Methyl 2-{[4-(3-chloro-4-{[(dimethylamino)carbonyl]amino}phenoxy)-6-methoxy-7-quinazolinyl]oxy}acetate

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-dimethylurea, 50 mg), potassium carbonate (138 mg), and bromoethyl acetate (49 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC by development with chloroform/methanol to give 37 mg (yield 60%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.07 (s, 6H), 3.82 (s,

3H), 4.06 (s, 3H), 4.87 (s, 2H), 6.97 (s, 1H), 7.14 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.18 (s, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.54 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.60 (s, 1H)

Example 182: N'-[2-Chloro-4-({6-methoxy-7-[3-(4-methylpiperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N,N-dimethylurea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-dimethylurea, 400 mg), potassium carbonate (966 mg), and 1,3-dibromopropane (0.51 ml) were dissolved in N,N-dimethylformamide (5 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 398 mg (yield 78%) of an intermediate (N'-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N,N-dimethylurea). The intermediate (51 mg), potassium carbonate (138 mg), and 1-methylpiperazine (0.055 ml) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 46 mg (yield 85%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.06 - 2.16 (m, 2H), 2.29 (s, 3H), 2.30 - 2.60 (m, 10H), 3.07 (s, 6H), 4.02 (s, 3H), 4.25 (t, J = 6.8 Hz, 2H), 6.96 (s, 1H), 7.15 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.30 (s, 1H), 7.48 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.59 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 529 (M^++1)

Example 183: N'-{2-Chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinazolinyl)oxy]-phenyl}-N,N-dimethylurea

A starting compound (N'-{2-chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N,N-dimethylurea, 400 mg), potassium carbonate (966 mg), and 1,3-dibromopropane (0.51 ml) were dissolved in N,N-dimethylformamide (5 ml), and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 398 mg (yield 78%) of an intermediate (N'-(4-{[7-(3-bromopropoxy)-6-methoxy-4-quinazolinyl]oxy}-2-chlorophenyl)-N,N-dimethylurea). The intermediate (51 mg), potassium carbonate (138 mg), and 2-(methylamino)ethanol (0.040 ml) were dissolved in N,N-dimethylformamide (1 ml). The mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 49 mg (yield 97%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.01 - 2.11 (m, 2H), 2.25 (s, 3H), 2.52 (t, J = 5.1 Hz, 2H), 2.61 (t, J = 7.1 Hz, 2H), 3.03 (s, 6H), 3.57 (t, J = 5.1 Hz, 2H), 3.98 (s, 3H), 4.23 (t, J = 6.6 Hz, 2H), 6.92 (s, 1H), 7.10 (dd, J = 2.7 Hz, 9.3 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 7.31 (s, 1H), 7.44 (s, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.54 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 504 (M^++1)

Example 184: N-(2-Chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-methylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinaz-

olinyl)oxy]phenyl}-N'-methylurea (2.0 g) was dissolved in N,N-dimethylformamide (50 ml), and triphenylphosphine (2.8 g), piperidinopropanol (0.9 g), and diethyl azodicarboxylate (1.9 g) were added to the solution. The mixture was stirred at room temperature for 2 hr. Triphenylphosphine (2.8 g), piperidinopropanol (0.6 g), and diethyl azodicarboxylate (1.9 g) were then again added to the reaction solution, followed by stirring at room temperature for additional 10 hr. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (20/1) to give 650 mg (yield 25%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.37 - 1.43 (m, 2H), 1.43 - 1.53 (m, 4H), 1.96 - 2.00 (m, 2H), 2.29 - 2.50 (m, 6H), 2.68 (d, J = 4.6 Hz, 3H), 3.97 (s, 3H), 4.23 (t, J = 6.3 Hz, 2H), 6.82 - 6.85 (m, 1H), 7.23 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.38 (s, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.54 (s, 1H), 8.07 (s, 1H), 8.17 (d, J = 9.0 Hz, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 500 (M^++1)

Example 185: N-(2-Chloro-4-{[6-methoxy-7-(3-piperidinopropoxy)-4-quinazolinyl]oxy}phenyl)-N'-ethylurea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinazolinyl)oxy]phenyl}-N'-ethylurea (2.7 g) was dissolved in N,N-dimethylformamide (30 ml), and triphenylphosphine(3.6 g), piperidinopropanol (1.2 g), and diethyl azodicarboxylate (2.4 g) were added to the solution. The mixture was stirred at room temperature for 2 hr. Triphenylphosphine(3.6 g), piperidinopropanol (0.8 g), and diethyl azodicarboxylate (1.9 g) were then again added to the reaction solution. The mixture was stirred at room temperature for additional 10 hr. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/methanol (20/1) to give 1.5 g (yield 42%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, J = 7.0 Hz, 3H), 1.38 - 1.41 (m, 2H), 1.47 - 1.53 (m, 4H), 1.95 - 2.00 (m, 2H), 2.31 - 2.46 (m, 6H), 3.10 - 3.17 (m, 2H), 3.97 (s, 3H), 4.23 (t, J = 6.3 Hz, 2H), 6.96 (t, J = 5.6 Hz, 1H), 7.23 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.37 (s, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.54 (s, 1H), 8.02 (s, 1H), 8.19 (d, J = 9.3 Hz, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 514 (M^++1)

Example 186: N-(2-Chloro-4-{[6-methoxy-7-(4-pyridylmethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)-oxy]phenyl}-N'-(2,4-difluorophenyl)urea (55 mg), potassium carbonate (62 mg), and 4-(chloromethyl)pyridine hydrochloride (22 mg) were dissolved in N,N-dimethylformamide (1 ml), and the solution was stirred at 80°C for one hr. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was washed with ether to give 35 mg (yield 55%) of the title compound.

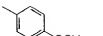
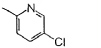
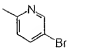
^{1}H-NMR (DMSO, 400 MHz): δ 3.98 (s, 3H), 5.41 (s, 2H), 6.56 (d, J = 5.1 Hz, 1H), 7.04 - 7.10 (m, 1H), 7.25 - 7.37 (m, 2H), 7.47 (s, 1H), 7.49 - 7.52 (m, 4H), 7.55 (s, 1H), 8.08 - 8.15 (m, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.60 - 8.63 (m, 1H), 8.81 - 8.83 (m, 1H), 9.30 - 9.31 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 563 (M^++1)

The structures of the compounds described in the examples are as follows.

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
1	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
2	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
3	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
4	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
5	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
6	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
7	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
8	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
9	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
10	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
11	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
12	CH	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
13	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
14	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
15	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
16	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
17	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
18	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
19	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
20	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
21	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
22	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
23	CH	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
24	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
25	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
26	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
27	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
28	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
29	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
30	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	

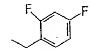
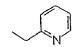
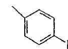
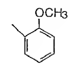
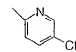
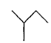
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
31	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
32	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
33	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
34	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
35	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
36	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
37	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
38	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
39	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
40	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
41	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
42	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
43	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
44	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
45	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
46	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
47	CH	CH	H	CH_3O	CH_3O	H	H	NO_2	H	H	H	H	
48	CH	CH	H	CH_3O	CH_3O	H	H	NO_2	H	H	H	H	
49	CH	CH	H	CH_3O	CH_3O	H	Cl	H	Cl	H	H	H	
50	CH	CH	H	CH_3O		H	H	F	H	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
51	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
52	CH	CH	H	CH_3O		H	H	CH_3	CH_3	H	H	H	
53	CH	CH	H	CH_3O		H	H	CH_3	CH_3	H	H	H	
54	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	Cl	H	H	H	H	
55	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	Cl	H	H	H	H	
56	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	CH_3	CH_3	H	H	H	H	
57	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	CH_3	CH_3	H	H	H	H	
58	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	CH_3	CH_3	H	H	H	
59	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	CH_3	CH_3	H	H	H	
60	CH	CH	H	CH_3O		H	CH_3	CH_3	H	H	H	H	

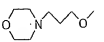
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
61	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
62	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
63	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
64	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
65	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
66	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
67	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
68	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
69	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
70	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	

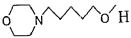
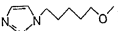
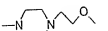
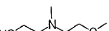
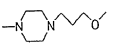
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
71	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
72	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
73	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
74	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
75	N	CH	H	CH_3O	CH_3O	H	H	H	H	H	H	H	
76	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
77	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
78	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
79	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
80	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	

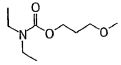
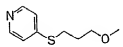
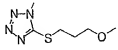
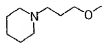
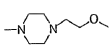
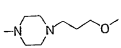
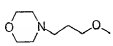
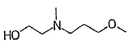
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
81	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
82	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
83	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
85	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
86	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
87	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	
88	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
89	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
90	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	

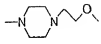
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
91	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
92	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
93	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
94	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
95	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
96	N	CH	H	CH_3O	CH_3O	H	H	F	H	H	H	H	
97	N	CH	H	CH_3O	CH_3O	H	CH_3	H	H	H	H	H	
98	N	CH	H	CH_3O	CH_3O	H	CH_3	H	H	H	H	H	
99	N	CH	H	CH_3O	CH_3O	H	CH_3	H	H	H	H	H	
100	N	CH	H	CH_3O	CH_3O	H	CH_3	H	H	H	H	H	

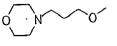
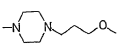
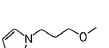
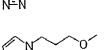
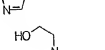
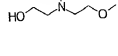
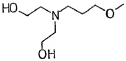
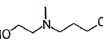
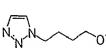
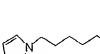
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
101	N	CH	H	CH_3O	CH_3O	H	CH_3	H	H	H	H	H	
102	N	CH	H	CH_3O	CH_3O	H	H	CH_3	H	H	H	H	
103	N	CH	H	CH_3O	CH_3O	H	H	CH_3	H	H	H	H	
104	N	CH	H	CH_3O	CH_3O	H	H	CH_3	H	H	H	H	
105	N	CH	H	CH_3O	CH_3O	H	H	CH_3	H	H	H	H	
106	N	CH	H	CH_3O	CH_3O	H	H	CH_3	H	H	H	H	
107	N	CH	H	CH_3O	CH_3O	H	H	NO_2	H	H	H	H	
108	N	CH	H	CH_3O	CH_3O	H	H	NO_2	H	H	H	H	
109	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	CH_2OCH_3	H	
110	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	$CH_3C(=O)-$	H	

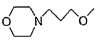
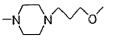
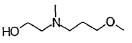
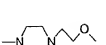
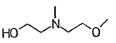
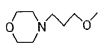
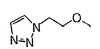
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
111	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	CH_3	
112	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	CH_3CH_2	
113	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	$CH_3(CH_2)_2$	
114	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	CH_3	
115	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	CH_3	
116	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	CH_3CH_2	
117	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	H	CH_3
118	N	CH	H	CH_3O	CH_3O	H	H	Cl	H	H	H	CH_3	CH_3
119	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
120	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	

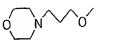
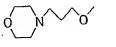
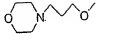
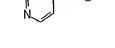
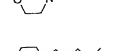
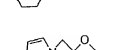
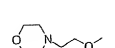
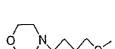
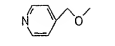
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
121	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
122	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
123	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
124	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
125	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
126	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3CH_2	
127	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
128	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
129	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
130	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	

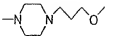
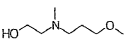
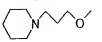
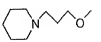
	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
131	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3CH_2	
132	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3CH_2	
133	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
134	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
135	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
136	N	CH	H		CH_3O	H	H	Cl	H	H	H	H	
137	N	CH	H		CH_3O	H	H	Cl	H	H	H	H	
138	N	CH	H		CH_3O	H	H	Cl	H	H	H	H	
139	N	CH	H		CH_3O	H	H	Cl	H	H	H	H	
140	N	CH	H		CH_3O	H	H	Cl	H	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
141	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
142	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
143	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
144	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
145	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
146	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
147	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
148	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
149	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
150	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
151	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
152	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
153	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
154	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
155	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
156	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
157	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
158	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
159	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
160	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
161	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
162	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
163	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
164	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
165	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
166	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
167	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
168	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
169	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	
170	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
171	N	CH	H	CH_3O		H	H	CH_3O	H	H	H	H	
172	N	CH	H	CH_3O		H	H	CH_3O	H	H	H	H	
173	CH	CH	H	CH_3O		H	H	CH_3O	H	H	H	H	
174	CH	CH	H	CH_3O		H	H	CH_3O	H	H	H	H	
175	CH	CH	H	CH_3O		H	H	CH_3	CH_3	H	H	H	
176	CH	CH	H	CH_3O		H	H	CH_3	CH_3	H	H	H	
177	CH	CH	H	CH_3O		H	H	CH_3	CH_3	H	H	H	
178	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3	CH_3
179	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3	CH_3
180	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3	CH_3

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
181	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3	CH_3
182	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3	CH_3
183	N	CH	H	CH_3O		H	H	Cl	H	H	H	CH_3	CH_3
184	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	CH_3
185	N	CH	H	CH_3O		H	H	Cl	H	H	H	H	
186	CH	CH	H	CH_3O		H	H	Cl	H	H	H	H	

Pharmacological Test Example 1: Measurement of inhibitory activity against activation of MAPK within vascular endothelial cells induced by VEGF stimulation

Human funicular venous vascular endothelial cells (purchased from Chronetics) were cultured in an EGM-2 medium (purchased from Chronetics) within an incubator containing 5% carbon dioxide until 50 to 70% confluent, and the culture was inoculated into wells, containing the same medium, in a 96-well flat-bottom plate in an amount of 1.5×10^5 per well. After cultivation at 37°C overnight, the medium was replaced by an EBM-2 medium containing 0.5% fetal calf serum (purchased from Chronetics), followed by cultivation for 24 hr. A solution of the test compound in dimethyl sulfoxide was added to each well, and the cultivation was continued at 37°C for additional one hr. A human recombinant vascular endothelial growth factor (hereinafter abbreviated to "VEGF") was added to a final concentration of 50 ng/ml, and the stimulation of cells was carried out at 37°C for 8 min. The medium was removed, the cells were washed with phosphate buffered saline (pH 7.4), and 10 µl of a solubilization buffer (Tris buffered saline (pH 7.4) containing 1% Triton X100, 2 mM sodium orthovanadylate, and 1 mM disodium ethylenediaminetetraacetate) was then added thereto. The mixture was shaken at 4°C for one hr to solubilize the cells. An equal amount of Tris buffered saline containing 1% sodium laurylsulfate was added to and thoroughly mixed with the solution. This solution (2 µl) was adsorbed on a PVDF filter by dot blotting, and this filter was subjected to immunoblotting with anti-tyrosine phosphorylated MAPK antibody (purchased from Daiichi Pure Chemicals).

The level of phosphorylated MAPK was quantitatively determined with a densitometer, and the percentage phosphorylated MAPK in the presence of the test compound was determined by presuming the level of phosphorylated MAPK with the addition of VEGF in the absence of the

test compound to be 100% and the level of phosphorylated MAPK in the absence of the test compound and VEGF to be 0%. The test compound concentration (IC_{50}) necessary for inhibiting 50% of the activation of MAPK was calculated based on the percentage of phosphorylated MAPK.

The results were as summarized in Table 1.

Table 1

Compound	IC_{50}(nM)	Compound	IC_{50}(nM)	Compound	IC_{50}(nM)
1	1.8	45	2.0	85	0.7
4	2.1	46	4.3	86	0.6
5	2.9	47	4.0	87	58.0
7	5.2	48	0.5	89	45.0
8	11.0	49	4.3	90	42.0
9	5.1	50	0.5	92	46.0
10	7.8	52	4.4	93	14.0
11	15.0	53	5.9	94	1.8
13	2.2	54	0.5	95	2.7
14	0.7	55	2.8	96	<1
16	2.9	56	5.1	97	518.0
17	11.0	57	6.5	98	450.0
18	0.6	58	5.1	99	8.8
19	0.6	59	5.8	100	5.2
20	8.5	62	16.0	102	150.0
21	3.4	63	70.0	103	53.0
22	0.4	64	42.0	104	5.3
23	5.4	65	36.0	105	2.3
24	0.6	66	21.0	106	<1
25	3.9	67	345.0	107	10.2
26	5.3	68	45.0		
28	4.0	69	67.0		
29	4.4	70	6.8		
30	1.7	71	750.0		
31	2.5	72	3.9		
32	7.3	73	<2		
33	3.5	74	6.0		
34	4.2	75	1.2		
35	3.7	76	8.0		
36	3.3	77	71.0		
37	2.3	78	4.1		
40	12.0	79	30.0		
41	4.9	80	13.0		
42	5.9	82	3.8		
43	3.8	83	>1000		

Pharmacological Test Example 2: Measurement of inhibitory activity against KDR phosphorylation by ELISA

NIH 3T3 cells (Sawano A et al., Cell Growth & Differentation, 7, 213-221 (1996), "Flt-1 but not

KDR/Flk-1 tyrosine kinase is a receptor for placenta growth factor, which is related to vascular endothelial growth factor") prepared by transfection of human KDR were cultured in a DMEM medium containing 10% fetal calf serum (purchased from GIBCO BRL) within a 5% carbon dioxide incubator until 50 to 70% confluent. The harvested cells were inoculated into wells, containing the same medium, in a collagen-type one-coat 96-well flat-bottom plate in an amount of 1.5×10^4 per well, followed by cultivation at 37°C overnight. The medium was then replaced by a DMEM medium containing 0.1% fetal calf serum. A solution of the test compound in dimethyl sulfoxide was added to each well, and the cultivation was continued at 37°C for additional one hr. A human recombinant vascular endothelial growth factor (hereinafter abbreviated to "VEGF") was added to a final concentration of 100 ng/ml, and the stimulation of cells was carried out at 37°C for 2 min. The medium was removed, the cells were washed with phosphate buffered saline (pH 7.4), and 50 µl of a solubilization buffer (20 mM HEPES (pH 7.4), 150 mM NaCl, 0.2% Triton X-100, 10% glycerol, 5 mM sodium orthovanadylate, 5 mM disodium ethylenediaminetetraacetate, and 2 mM $Na_4P_2O_7$) was then added thereto. The mixture was shaken at 4°C for 2 hr to prepare a cell extract.

Separately, phosphate buffered saline (50 µl, pH 7.4) containing 5 µg/ml of anti-phospho-tyrosine antibody (PY20; purchased from Transduction Laboratories) was added to a microplate for ELISA (Maxisorp; purchased from NUNC), followed by standing at 4°C overnight to form a solid phase on the wells. After washing of the plate, 300 µl of a blocking solution was added, followed by standing at room temperature for 2 hr to perform blocking. After washing, the whole quantity of the cell extract was transferred to the wells, and the plate was then allowed to stand at 4°C overnight. After washing, an anti-KDR antibody (purchased from

Santa Cruz) was allowed to react at room temperature for one hr, and, after washing, a peroxidase-labeled anti-rabbit Ig antibody (purchased from Amersham) was allowed to react at room temperature for one hr. After washing, a chromophoric substrate for peroxidase (purchased from Sumitomo Bakelite Co., Ltd.) was added thereto to initiate a reaction. After a suitable level of color development, a reaction termination solution was added to stop the reaction, and the absorbance at 450 nm was measured with a microplate reader. The KDR phosphorylation activity for each well was determined by presuming the absorbance with the addition of VEGF and without the addition of the medicament to be 100% KDR phosphorylation activity and the absorbance without the medicament and VEGF to be 0% KDR phosphorylation activity. The concentration of the test compound was varied on several levels, the inhibition (%) of KDR phosphorylation was determined for each case, and the concentration of the test compound necessary for inhibiting 50% of KDR phosphorylation (IC_{50}) was calculated.

The results were as summarized in Table 2.

Table 2

Compound	IC_{50}(nM)	Compound	IC_{50}(nM)	Compound	IC_{50}(nM)
62	11.0	103	78.0	146	1.0
63	150.0	104	3.9	147	1.0
64	150.0	105	2.0	148	15.0
65	27.0	106	1.5	149	1.6
66	15.0	107	11.0	150	1.8
67	63.0	108	5.0	151	0.5
68	24.0	110	>1000	152	0.8
69	64.0	111	>1000	153	1.5
70	32.0	112	>1000	154	1.5
71	350.0	113	>1000	155	2.1
72	3.5	114	>1000	156	0.8
73	1.0	115	>1000	157	0.4
74	11.0	116	>1000	158	1.6
75	1.4	117	24.0	159	1.9
76	3.5	118	>1000	160	0.9
77	6.0	119	3.6	161	3.9
78	3.4	120	3.9	162	1.0
79	18.0	121	12.5	163	1.4
80	2.7	122	5.8	164	0.9
81	4.1	123	8.9	165	0.6
82	8.4	124	1.9	166	2.2
83	840.0	125	2.6	167	2.1
85	0.5	126	>1000	168	4.0
86	1.5	127	1.1	169	3.7
87	110.0	131	>1000	170	1.1
88	61.0	132	>1000	175	4.7
89	24.0	133	8.3	176	3.7
90	57.0	134	5.0	177	2.3
92	63.0	135	1.0	178	>1000
93	37.0	136	160.0	179	>1000
94	2.3	137	24.0	180	>1000
95	3.8	138	40.0	181	>1000
96	0.4	139	15.0	182	>1000
97	490.0	140	36.0	183	>1000
98	330.0	141	14.0	184	0.2
99	25.0	142	2.6	185	0.5
100	13.0	143	3.5	186	6.3
101	3.0	144	1.6		
102	105.0	145	0.8		

Pharmacological Test Example 3: Karyomorphosis test

A375 human melanoma cells (2×10^4) (obtained from Japanese Foundation for Cancer Research) were incolulated on a culture slide (manufactured by Falcon) and were cultured at 37°C. After the elapse of 5 hr from the initiation of the cultivation, the test compound was added to 10 μM and 1 μM, and the cultivation was continued for additional 48 hr. After the fixation of cells, 50 μg/ml propidium iodide solution containing ribonuclease (200 μg/ml) was added to stain nuclei. The stained nuclei were observed under a fluorescent microscope to analyze the nuclei for abnormality of karyomorphosis. The change in karyomorphosis for test compounds was evaluated as (2+) when the change in karyomorphosis of cells took place at 1 μM; was evaluated as (+) when the change in karyomorphosis of cells took place at 10 μM; and was evalauted as (-) when the change in karyomorphosis of cells did not take place at 10 μM.

The results were as summarized in Table 3.

Table 3

Compound No.	Change in morphosis	Compound No.	Change in morphosis
13	(-)	37	(-)
14	(-)	38	(-)
15	(-)	39	(-)
16	(-)	40	(-)
17	(-)	41	(-)
18	(-)	42	(-)
20	(-)	43	(-)
21	(-)	44	(-)
22	(-)	45	(-)
24	(-)	46	(-)
25	(-)	47	(-)
26	(-)	48	(-)
28	(-)	49	(-)
29	(-)	52	(-)
30	(-)	53	(-)
31	(-)	55	(-)
32	(-)	58	(-)
33	(-)	59	(-)
34	(-)	60	(-)
35	(-)	61	(-)
36	(-)	62	(-)

<u>Pharmacological Test Example 4: Antitumor effect on human glioma cells (GL07)</u>

Human glioma cells GL07 (obtained from Central Laboratories for Experimental Animals) were transplanted into nude mice. When the tumor volume became about 100 mm^3, the mice were grouped. In this case, grouping was carried out so that each group consisted of four mice and the average tumor volume was even among the groups. The test compound was orally or intraperitoneally administered at a dose of 20 mg/kg to the test groups every day once a day for 9 days, while the medium was administered to the control group in the manner as in the test groups. The tumor growth inhibition rate (TGIR) was calculated as follows: The tumor growth inhibition rate (TGIR) = (1 - Tx/Cx) x 100 wherein Cx represents the volume of tumor at day x for the control group when

the tumor volume at the day of the start of the administration was presumed to be 1; and Tx represents the volume of tumor for test compound administration groups.

The tumor growth inhibition rate for representative examples of a group of compounds according to the present invention is shown in Table 4.

Table 4 (Part 1)

Ex. No.	Administration site	TGIR, %	Ex. No.	Administration site	TGIR, %	Ex. No.	Administration site	TGIR, %
4	Oral	61	102	Oral	24	147	Oral	34
5	Oral	59	103	Oral	23	148	Oral	54
9	Intraperitoneal	59	104	Oral	22	149	Oral	47
13	Intraperitoneal	52	105	Oral	20	150	Oral	22
14	Intraperitoneal	81	107	Oral	49	151	Oral	44
16	Intraperitoneal	77	109	Oral	71	152	Oral	44
17	Intraperitoneal	85	110	Oral	26	153	Oral	53
18	Oral	57	111	Oral	78	154	Oral	34
24	Oral	63	112	Oral	81	155	Oral	29
25	Intraperitoneal	68	113	Oral	61	156	Oral	24
28	Intraperitoneal	84	114	Oral	60	157	Oral	44
29	Oral	64	115	Oral	74	158	Oral	39
37	Intraperitoneal	70	116	Oral	83	159	Oral	40
48	Intraperitoneal	90	119	Oral	40	160	Oral	43
50	Oral	59	120	Oral	30	161	Oral	39
51	Oral	65	121	Oral	22	162	Oral	40
54	Oral	59	122	Oral	21	163	Oral	52
62	Oral	78	123	Oral	31	164	Oral	55
64	Oral	37	124	Oral	27	165	Oral	44
66	Oral	26	125	Oral	30	166	Oral	27

TGIR, % = Tumor growth inhibition rate (%)

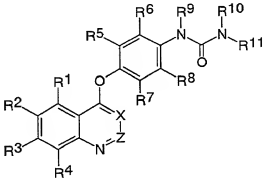
Table 4 (Part 2)

Ex. No.	Administration site	TGIR, %	Ex. No.	Administration site	TGIR, %	Ex. No.	Administration site	TGIR, %
67	Oral	30	126	Oral	52	167	Oral	28
68	Oral	57	127	Oral	25	168	Oral	42
69	Oral	26	128	Oral	21	169	Oral	55
71	Oral	67	129	Oral	25	170	Oral	64
73	Oral	34	130	Oral	32	171	Oral	13
74	Oral	28	131	Oral	31	172	Oral	42
77	Oral	26	132	Oral	24	173	Oral	21
78	Oral	21	133	Oral	20	174	Oral	19
79	Oral	28	134	Oral	29	175	Oral	17
80	Oral	52	135	Oral	62	176	Oral	22
82	Oral	27	136	Oral	23	177	Oral	35
83	Oral	31	137	Oral	20	178	Oral	28
85	Oral	26	138	Oral	21	179	Oral	33
89	Oral	40	139	Oral	27	180	Oral	45
93	Oral	29	140	Oral	21	181	Oral	21
94	Oral	29	141	Oral	28	182	Oral	31
97	Oral	48	142	Oral	48	183	Oral	22
98	Oral	38	143	Oral	53	184	Oral	48
99	Oral	33	144	Oral	56	185	Oral	59
100	Oral	36	145	Oral	57	186	Oral	47
101	Oral	44	146	Oral	48			

TGIR, % = Tumor growth inhibition rate (%)

CLAIMS

1. A compound represented by formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

X and Z each represent CH or N;

R^1, R^2, and R^3, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, nitro, or amino, which C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted by a halogen atom; hydroxyl; C_{1-4} alkoxy; C_{1-4} alkoxycarbonyl; amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl or C_{1-4} alkoxy; group $R^{12}R^{13}N$-C(=O)-O- wherein R^{12} and R^{13}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkyl which alkyl is optionally substituted by hydroxyl or C_{1-4} alkoxy; or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group optionally substituted by C_{1-4} alkyl and m is 0 or 1;

R^4 represents a hydrogen atom;

R^5, R^6, R^7, and R^8, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino, provided that R^5, R^6, R^7, and R^8 do not simultaneously represent a hydrogen atom;

R^9 and R^{10}, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, or C_{1-4} alkylcarbonyl, the alkyl portion of which C_{1-6} alkyl or C_{1-4} alkylcarbonyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group; and

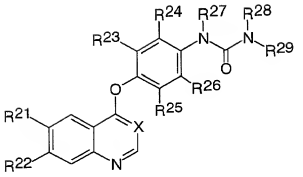
R^{11} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-6} alkoxy), or R^{15}-(CH_2)n- wherein n is an integer of 0 to 4 and R^{15} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-6} alkyl, or C_{1-6} alkoxy and is optionally condensed with other saturated or unsaturated three- to seven-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

2. The compound according to claim 1, wherein R^1, R^9, and R^{10} represent a hydrogen atom.

3. The compound according to claim 1, wherein R^1 represents a hydrogen atom and one of or both R^9 and R^{10} represent a group other than a hydrogen atom.

4. The compound according to claim 1, wherein X represents N or CH and Z represents CH.

5. A compound represented by formula (Ia) or a pharmaceutically acceptable salt or solvate thereof:



(Ia)

wherein

X represents CH or N;

R^{21} and R^{22}, which may be the same or different, represent unsubstituted C_{1-6} alkoxy or group R^{31}-(CH_2)p-O- wherein R^{31} represents a halogen atom, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl or C_{1-4} alkoxy, group $R^{12}R^{13}$N-C(=O)-O- wherein R^{12} and R^{13}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkyl which alkyl is optionally substituted by hydroxyl or C_{1-4} alkoxy, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group optionally substituted by C_{1-4} alkyl and m is 0 or 1; and p is an integer of 1 to 6;

R^{23}, R^{24}, R^{25}, and R^{26}, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino, provided that R^{23}, R^{24}, R^{25}, and R^{26} do not simultaneously represent a hydrogen atom;

R^{27} and R^{28}, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, or C_{1-4} alkylcarbonyl, the alkyl portion of which C_{1-6} alkyl or C_{1-4} alkylcarbonyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or a saturated or unsaturated three- to seven-membered

carbocyclic or heterocyclic group; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or R^{32}-$(CH_2)q$- wherein q is an integer of 0 to 4 and R^{32} represents a saturated or unsaturated six-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-6} alkyl, or C_{1-4} alkoxy and is optionally condensed with other saturated or unsaturated five- or six-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

6. The compound according to claim 5, wherein R^{21} and R^{22} represent unsubstituted C_{1-4} alkoxy.

7. The compound according to claim 5, wherein any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group R^{31}-$(CH_2)p$-O-.

8. The compound according to claim 5, wherein at least one of R^{23}, R^{24}, R^{25}, and R^{26} represents a halogen atom.

9. The compound according to claim 5, wherein at least one of R^{23}, R^{24}, R^{25}, and R^{26} represents a chlorine atom or a fluorine atom.

10. The compound according to claim 5, wherein at least one of R^{23}, R^{24}, R^{25}, and R^{26} represents C_{1-4} alkyl.

11. The compound according to claim 5, wherein two of R^{23}, R^{24}, R^{25}, and R^{26} represent methyl and the remaining two represent a hydrogen atom.

12. The compound according to claim 5, wherein at least one of R^{23}, R^{24}, R^{25}, and R^{26} represents nitro, amino,

C_{1-4} alkoxy, or C_{1-4} alkylthio.

13. The compound according to claim 5, wherein R^{23}, R^{25}, and R^{26} represent a hydrogen atom and R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, or amino.

14. The compound according to claim 5, wherein both R^{27} and R^{28} represent a hydrogen atom.

15. The compound according to claim 5, wherein any one of or both R^{27} and R^{28} represent a group other than a hydrogen atom.

16. The compound according to claim 5, wherein

X represents CH or N;

R^{21} and R^{22} represent unsubstituted C_{1-4} alkoxy;

R^{23}, R^{25}, and R^{26} represent a hydrogen atom;

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro;

R^{27} and R^{28} represent a hydrogen atom; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

17. The compound according to claim 5, wherein

X represents CH or N;

R^{21} and R^{22} represent unsubstituted C_{1-4} alkoxy;

R^{23}, R^{25}, and R^{26} represent a hydrogen atom;

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro;

any one of or both R^{27} and R^{28} represent a group other than a hydrogen atom; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6}

alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

18. The compound according to claim 5, wherein

X represents CH or N;

R^{21} and R^{22} represent unsubstituted C_{1-4} alkoxy;

R^{23}, R^{25}, and R^{26} represent a hydrogen atom;

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro;

R^{27} represents a hydrogen atom;

R^{28} represents a group other than a hydrogen atom; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

19. The compound according to claim 5, wherein

X represents CH or N;

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group $R^{31}-(CH_2)p-O-$;

R^{23}, R^{25}, and R^{26} represent a hydrogen atom;

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro;

R^{27} and R^{28} represent a hydrogen atom; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which

phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

20. The compound according to claim 19, wherein R^{21} represents unsubstituted C_{1-4} alkoxy and R^{22} represents group R^{31}-$(CH_2)p$-O-.

21. The compound according to claim 19 or 20, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

22. The compound according to any one of claims 19 to 21, wherein p is 1.

23. The compound according to any one of claims 19 to 21, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

24. The compound according to any one of claims 19 to 21, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

25. The compound according to claim 23 or 24,

wherein R^{14} represents optionally substituted pyridyl.

26. The compound according to claim 5, wherein

X represents CH or N;

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group R^{31}-(CH_2)p-O-;

R^{23}, R^{25}, and R^{26} represent a hydrogen atom;

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro;

any one of or both R^{27} and R^{28} represent a group other than a hydrogen atom; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)q-R^{32}$ wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

27. The compound according to claim 26, wherein R^{21} represents unsubstituted C_{1-4} alkoxy and R^{22} represents group R^{31}-(CH_2)p-O-.

28. The compound according to claim 26 or 27, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

29. The compound according to any one of claims 26

to 28, wherein p is 1.

30. The compound according to any one of claims 26 to 28, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

31. The compound according to any one of claims 26 to 28, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

32. The compound according to claim 30 or 31, wherein R^{14} represents optionally substituted pyridyl.

33. The compound according to claim 5, wherein

X represents CH or N;

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group R^{31}-(CH_2)p-O-;

R^{23}, R^{25}, and R^{26} represent a hydrogen atom;

R^{24} represents a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro;

R^{27} represents a hydrogen atom;

R^{28} represents a group other than a hydrogen atom; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or -(CH_2)q-R^{32} wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

34. The compound according to claim 33, wherein R^{21}

represents unsubstituted C_{1-4} alkoxy and R^{22} represents group R^{31}-(CH_2)p-O-.

35. The compound according to claim 33 or 34, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

36. The compound according to any one of claims 33 to 35, wherein p is 1.

37. The compound according to any one of claims 33 to 35, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

38. The compound according to any one of claims 33 to 35, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

39. The compound according to claim 37 or 38, wherein R^{14} represents optionally substituted pyridyl.

40. The compound according to claim 5, wherein X represents CH or N;

any one of R^{21} and R^{22} represents unsubstituted C_{1-4} alkoxy and the other represents group R^{31}-(CH_2)p-O-;

R^{23} and R^{26} represent a hydrogen atom;

R^{24} and R^{25} represent a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, or nitro;

R^{27} and R^{28} represent a hydrogen atom;

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or -(CH_2)q-R^{32} wherein q is an integer of 0 or 1 and R^{32} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

41. The compound according to claim 40, wherein R^{21} represents unsubstituted C_{1-4} alkoxy and R^{22} represents group R^{31}-(CH_2)p-O-.

42. The compound according to claim 40 or 41, wherein R^{31} represents hydroxyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated five-membered heterocyclic group containing 1 to 4 nitrogen atoms and optionally substituted by C_{1-4} alkyl, or a saturated or unsaturated six-membered heterocyclic group containing one or two hetero-atoms selected from nitrogen and oxygen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero); and p is an integer of 1 to 4.

43. The compound according to any one of claims 40 to 42, wherein p is 1.

44. The compound according to any one of claims 40 to 42, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic

group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero).

45. The compound according to any one of claims 40 to 42, wherein R^{31} represents group R^{14}-(S)m- wherein R^{14} represents an unsaturated six-membered heterocyclic group containing one or two nitrogen atoms and optionally substituted by C_{1-4} alkyl and m is 0 (zero) and p is 1.

46. The compound according to claim 44 or 45, wherein R^{14} represents optionally substituted pyridyl.

47. The compound according to claim 1, which is a compound selected from the group consisting of the following compounds, or a pharmaceutically acceptable salt or solvate thereof:

(13) N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(51) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl) urea;

(62) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-propylurea;

(76) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}-N'-ethylurea;

(117) N-{2-chloro-4-[(6,7-dimethoxy-4-quinazo-linyl)oxy]phenyl}-N'-methylurea;

(119) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

(135) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-propylurea;

(142) N-(2-chloro-4-{[6-methoxy-7-(3-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(143) N-(2-chloro-4-{[6-methoxy-7-(4-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(144) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-

ethoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(145) N-[2-chloro-4-{(6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(146) N-[2-chloro-4-(7-{[2-(1H-1-imidazolyl)-ethoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(148) N-[2-chloro-4-(6-methoxy-7-{[2-(4-methyl-piperazino)ethoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(149) N-(2-chloro-4-{[7-(2-hydroxyethoxy)-6-methoxy-4-quinolyl]oxy}phenyl)-N'-propylurea;

(151) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinolyl]oxy}phenyl)-N'-propylurea;

(152) N-[2-chloro-4-(6-methoxy-7-{[3-(4-methyl-piperazino)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(153) N-[2-chloro-4-(6-methoxy-7-{[3-(1*H*-1,2,3-triazol-1-yl)propoxy]-4-quinolyl}oxy)phenyl]-N'-propylurea;

(157) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinolyl)oxy]-phenyl}-N'-propylurea;

(159) N-{2-chloro-4-[(6-methoxy-7-{[5-(1*H*-1,2,3-triazol-1-yl)pentyl]oxy}-4-quinolyl)oxy]phenyl}-N'-propylurea;

(160) N-[2-chloro-4-(7-{[4-(1*H*-1-imidazolyl)-butoxy]-6-methoxy-4-quinolyl}oxy)phenyl]-N'-propylurea;

(162) N-(2-chloro-4-{[6-methoxy-7-(2-morpholino-ethoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(163) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-(2,4-difluoro-phenyl)urea;

(164) N-[2-chloro-4-(6-methoxy-7-{[3-(4-methyl-piperazino)propoxy]-4-quinazolinyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(165) N-{2-chloro-4-[(7-{3-[(2-hydroxyethyl)-(methyl)amino]propoxy}-6-methoxy-4-quinazolinyl)oxy]-

phenyl}-N'-(2,4-difluorophenyl)urea;

(168) N-(2-chloro-4-{[6-methoxy-7-(3-morpholino-propoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(169) N-(2-chloro-4-{[6-methoxy-7-(3-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea;

(170) N-[2-chloro-4-(6-methoxy-7-{[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinolyl}oxy)phenyl]-N'-(2,4-difluorophenyl)urea;

(184) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-methylurea;

(185) N-(2-chloro-4-{[6-methoxy-7-(3-piperidino-propoxy)-4-quinazolinyl]oxy}phenyl)-N'-ethylurea; and

(186) N-(2-chloro-4-{[6-methoxy-7-(4-pyridyl-methoxy)-4-quinolyl]oxy}phenyl)-N'-(2,4-difluorophenyl)-urea.

48. A pharmaceutical composition comprising as active ingredient the compound according to any one of claims 1 to 47 or a pharmaceutically acceptable salt or solvate thereof.

49. The pharmaceutical composition according to claim 48, for use in the treatment of a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma.

50. Use of the compound according to any one of claims 1 to 47 or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a therapeutic agent for use in the treatment of a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma.

51. A method for treating a disease selected from the group consisting of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, comprising the step of administering an effective amount of the compound according to any one of claims 1 to 47 or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier, to mammals.

52. A method for inhibiting the angiogenesis of target blood vessels, comprising the step of making the compound according to any one of claims 1 to 47 or a pharmaceutically acceptable salt or solvate thereof in contact with vascular endothelial cells of the target blood vessels.

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Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

私は、以下に記名された発明者として、ここに下記の通り宣言する：	As a below named inventor, I hereby declare that:
私の住所、郵便の宛先そして国籍は、私の氏名の後に記載された通りである。	My residence, post office address and citizenship are as stated next to my name.
下記の名称の発明について特許請求範囲に記載され、且つ特許が求められている発明主題に関して、私が最初、最先且つ唯一の発明者である（唯一の氏名が記載されている場合）か、或いは最初、最先且つ共同発明者である（複数の氏名が記載されている場合）と信じている。	I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled QUINOLINE DERIVATIVES AND QUINAZOLINE DERIVATIVES
上記発明の明細書はここに添付されているが、下記の欄がチェックされている場合は、この限りでない：	the specification of which is attached hereto unless the following box is checked:
☐ の日に出願され、 この出願の米国出願番号または PCT 出願番号は、 であり、且つ、 の日に訂正された出願（該当する場合）	☒ was filed on January 20, 2000 as United States Application Number or PCT International Application Number PCT/JP00/00255 and was amended on (if applicable).
私は、上記の補正書によって補正された、特許請求範囲を含む上記明細書を検討し、且つ内容を理解していることをここに表明する。	I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
私は、連邦規則法典第３７編規則１．５６に定義されている、特許性について重要な情報を開示する義務があることを認める。	I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

Japanese Language Declaration
(日本語宣言書)

私は、ここに、以下に記載した外国での特許出願または発明者証の出願、或いは米国以外の少なくとも一国を指定している米国法典第３５編第３６５条(ａ)によるＰＣＴ国際出願について、同第１１９条（ａ）－（ｄ)項又は第３６５条(ｂ)項に基づいて優先権を主張するとともに、優先権を主張する本出願の出願日よりも前の出願日を有する外国での特許出願または発明者証の出願、或いはＰＣＴ国際出願については、いかなる出願も、下記の枠内をチェックすることにより示した。

I hereby claim foreign priority under Title 35, United States Code, Section 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

外国での先行出願/Prior Foreign Application(s)

(番号) /(Number)	(国名) /(Country)	(出願年月日) /(Day/Month/Year Filed)	Priority Not Claimed 優先権主張なし
11-014858	Japan	22/January/1999	☐
11-026691	Japan	3/February/1999	☐
11-142493	Japan	21/May/1999	☐
11-253624	Japan	7/September/1999	☐
			☐
			☐
			☐

私は、ここに、下記のいかなる米国仮特許出願ついても、その米国法典第３５編１１９条(ｅ)項の利益を主張する。

I hereby claim the benefit under Title 35, United States Code, Section 119 (e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Application No.) (出願番号)	(Filing Date) (出願日)

私は、ここに、下記のいかなる米国出願についても、その米国法典第３５編第１２０条に基づく利益を主張し、又米国を指定するいかなるＰＣＴ国際出願についても、その同第３６５条(ｃ)に基づく利益を主張する。また、本出願の各特許請求の範囲の主題が米国法典第３５編第１１２条第１段に規定された態様で、先行する米国特許出願又はＰＣＴ国際出願に開示されていない場合においては、その先行出願の出願日と本国内出願日またはＰＣＴ国際出願日との間の期間中に入手された情報で、連邦規則法典第３７編規則１．５６に定義された特許性に関わる重要な情報について開示義務があることを承認する。

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or 365 (c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1 56 which became available between the filing date of the prior application and the national or PCT International filing date of application:

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)

私は、ここに表明された私自身の知識に係わる陳述が真実であり、且つ情報と信ずることに基づく陳述が、真実であると信じられることを宣言し、さらに、故意に虚偽の陳述などを行った場合は、米国法典第１８編第１００１条に基づき、罰金または拘禁、若しくはその両方により処罰され、またそのような故意による虚偽の陳述は、本出願またはそれに対して発行されるいかなる特許も、その有効性に問題が生ずることを理解した上で陳述が行われたことを、ここに宣言する。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration
(日本語宣言書)

委任状： 私は本出願を審査する手続を行い、且つ米国特許商標庁との全ての業務を遂行するために、記名された発明者として、下記の弁護士及び／または弁理士を任命する。（氏名及び登録番号を記載すること）

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POWER OF ATTORNEY. As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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Japanese Language Declaration
(日本語宣言書)

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国籍 日本		Citizenship
私書箱		Post Office Address
第五共同発明者		Full name of fifth joint inventor, if any
第五共同発明者の署名	日付	Fifth inventor's signature Date
住所 日本国.		Residence
国籍 日本		Citizenship
私書箱		Post Office Address
第六共同発明者		Full name of sixth joint inventor, if any
第六共同発明者の署名	日付	Sixth inventor's signature Date
住所 日本国.		Residence
国籍 日本		Citizenship
私書箱		Post Office Address
(第七以降の共同発明者についても同様に記載し、署名をすること)		(Supply similar information and signature for seventh and subsequent joint inventors)